

## Complete Summary

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### GUIDELINE TITLE

The pharmacologic management of chronic heart failure.

### BIBLIOGRAPHIC SOURCE(S)

Veterans Health Administration, Department of Veterans Affairs. The pharmacologic management of chronic heart failure. Washington (DC): Veterans Health Administration, Department of Veterans Affairs; 2003 Aug. 45 p. [242 references]

### GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Veterans Health Administration, Department of Veterans Affairs. The pharmacologic management of chronic heart failure. Washington (DC): Veterans Health Administration, Department of Veterans Affairs; 2002 Dec. 44 p.

## COMPLETE SUMMARY CONTENT

SCOPE  
 METHODOLOGY - including Rating Scheme and Cost Analysis  
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 INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT  
 CATEGORIES  
 IDENTIFYING INFORMATION AND AVAILABILITY  
 DISCLAIMER

## SCOPE

### DISEASE/CONDITION(S)

Chronic heart failure

### GUIDELINE CATEGORY

Diagnosis  
 Evaluation

Management  
Treatment

#### CLINICAL SPECIALTY

Cardiology  
Family Practice  
Internal Medicine  
Nursing

#### INTENDED USERS

Advanced Practice Nurses  
Nurses  
Physician Assistants  
Physicians

#### GUIDELINE OBJECTIVE(S)

- To present updated evidence-based pharmacologic guidelines on the management of chronic heart failure
- To assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing
- To present guidelines to serve as a basis for monitoring local, regional, and national patterns of pharmacological care

#### TARGET POPULATION

Veterans with chronic heart failure

#### INTERVENTIONS AND PRACTICES CONSIDERED

##### Evaluation/Diagnosis

1. Medical history and physical examination in a patient at risk for or suspected of having heart failure
2. Evaluation and diagnosis of patient suspected of having heart failure
  - Analysis of venous blood sample for creatinine, blood urea nitrogen, serum electrolytes including calcium and magnesium, urinalysis, complete blood count, fasting lipid profile, liver function tests, thyroid-stimulating hormone and possibly serum iron and saturation to exclude hemochromatosis
  - Electrocardiogram to assess for prior myocardial infarction (MI), voltage criteria suggestive of left ventricular hypertrophy (LVH), cardiac rhythm
  - Chest radiography to identify signs of volume overload or pulmonary disease
  - Evaluation of left ventricular function: 2-dimensional echocardiogram with Doppler flow studies; radionuclide ventriculography; cardiac catheterization

- Classification of heart failure using The American College of Cardiology/American Heart Association (ACC/AHA) staging of heart failure (A-D)
- Classification of heart failure using the New York Heart Association (NYHA) functional classification that estimates the severity of disease

## Management/Treatment

1. Nonpharmacologic interventions (abstaining from tobacco, alcohol, and illicit drug use; dietary measures to maintain fluid balance; reduction in weight if indicated; exercise; education on heart failure and treatment related to heart failure)
2. Avoidance of certain medications
3. Management of concomitant cardiac conditions and risk factors
4. Treatment of underlying causes of heart failure
5. Pharmacologic management of heart failure due to diastolic dysfunction
  - Measures to control blood pressure
  - Diuretics in patients with symptoms of volume overload
  - Drugs that control ventricular rate in patients with atrial fibrillation
  - Digoxin in patients with diastolic dysfunction in the absence of atrial fibrillation
  - Beta-adrenergic blockers, calcium channel blockers (CCBs), angiotensin-converting enzyme inhibitors (ACEI), angiotensin II receptor antagonists (AIIIRAs) in patients with controlled blood pressure who continue to have symptoms
  - Nitrates in patients with diastolic dysfunction as a result of coronary artery disease
6. Pharmacologic management of patients with asymptomatic systolic dysfunction
  - ACEI in patients with acute, recent, or history of MI
  - ACEI in patients with reduced left ventricular ejection fraction (LVEF)
  - Beta-adrenergic blocker in patients with acute, recent, or history of MI
  - Beta-adrenergic blocker in patients with reduced LVEF

Note: Guideline developers considered but did not recommend digoxin in patients with asymptomatic left ventricular dysfunction in sinus rhythm.

7. Assessment for signs and symptoms of volume overload in patients with systolic dysfunction
8. Pharmacologic management of patient with systolic heart failure
  - Diuretic therapy (loop diuretics, thiazide diuretics, thiazide-related diuretics) including: loop diuretics (furosemide, bumetanide, torsemide) in patients with evidence of fluid overload; combination of loop diuretic and either thiazide (hydrochlorothiazide, chlorthalidone) or metolazone in patients refractory to loop diuretic
  - Angiotensin-converting enzyme inhibitors (ACEIs) (captopril, enalapril, fosinopril, lisinopril)
  - Beta-adrenergic blockers (metoprolol XL, bisoprolol), alpha & beta antagonist (carvedilol)
  - Angiotensin II receptor antagonists (AIIIRAs) (eprosartan, candesartan, irbesartan, losartan, olmesartan, telmisartan, valsartan)

- including AIIRA in patients on standard therapy who cannot tolerate an ACEI due to cough and possibly, angioedema; AIIRA in addition to an ACEI in patients with heart failure, if not on a beta-adrenergic blocker.
  - Hydralazine/isosorbide dinitrate (HYD/ISDN) (hydralazine [HYD]; isosorbide dinitrate [ISDN]) including: HYD/ISDN in patients intolerant to ACEIs; HYD/ISDN in patients already taking an ACEI and B-adrenergic blocker.
  - Digoxin to improve functional status and reduce frequency of hospitalizations if continued symptoms on a diuretic and ACEI
  - Aldosterone antagonists (e.g., spironolactone) in patients with severe heart failure with normal potassium and adequate renal function
9. Follow-up of patients with systolic heart failure, including monitoring of electrolytes and renal function, assessment of adherence to medication regime, patient and family education as needed
  10. Referral, as indicated, to specialists or heart failure management program

## MAJOR OUTCOMES CONSIDERED

- Symptoms
- Functional capacity
- Quality of life
- Disease progression
- Need for hospitalization
- Survival rates

## METHODOLOGY

### METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)  
 Hand-searches of Published Literature (Secondary Sources)  
 Searches of Electronic Databases

### DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Development of the recommendations included reference to the following consensus document: Hunt SA, Baker DW, Chin MH, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure). 2001. American College of Cardiology Web site. Available at: [http://www.acc.org/clinical/guidelines/failure/hf\\_index.htm](http://www.acc.org/clinical/guidelines/failure/hf_index.htm).

The algorithm and annotations are in part based on the heart failure (HF) recommendations developed in 1997 and updated 2001. To update this information, the literature following the publication of the 2001 document was searched (search queried articles January 2001 to November 2002). A literature search of the National Library of Medicine's MEDLINE/PubMed database and Evidence Based Medicine reviews available on OVID was conducted. The following search terms were used: heart failure, angiotensin-converting enzyme inhibitor, beta-adrenergic blocker, digoxin, spironolactone, angiotensin receptor blocker,

calcium channel blocker, diastolic dysfunction, side effect, clinical trial, review, meta-analysis. The literature was limited to adult human subjects and articles published in the English language. The bibliographies of articles and consensus documents were reviewed for additional relevant literature. In updating the December 2002 document, 206 abstracts and 87 articles were reviewed. Sixty-four articles were added to the update of this document, 16 of which were randomized controlled trials. In addition to randomized controlled trials of patients with a diagnosis of chronic heart failure, the references added to the annotations discussing recommendations for specific pharmacologic classes included 11 pertinent subgroup analyses, 6 meta-analyses of controlled trials relevant to the recommendations in the document, and 9 review articles, some that provided a comprehensive inclusion of information and others that discussed patient care considerations not addressed by clinical trials. Literature known to the Pharmacy Benefits Management-Medical Advisory Panel (PBM-MAP) on medical history, physical examination, diagnosis, and evaluation was also included in the document. Since publication of the December 2002 iteration, two major articles were added to the August 2003 update.

#### NUMBER OF SOURCE DOCUMENTS

Not stated

#### METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

#### RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

The rating scale used for this document was based on the evidence rating of the U.S. Preventive Services Task Force.

##### Quality of Evidence

I: Evidence obtained from at least one properly randomized controlled trial

II-1: Evidence obtained from well-designed controlled trials without randomization

II-2: Evidence obtained from well-designed cohort or case-control analytic studies

II-3: Evidence obtained from multiple time series studies

III: Opinions of respected authorities, descriptive studies and case reports; reports of expert committees

##### Overall Quality

Good: High grade evidence (I or II-1) directly linked to health outcome

Fair: High grade evidence (I or II-1) linked to intermediate outcome or moderate grade evidence (II-2 or II-3) directly linked to health outcome

Poor: Level III evidence or no linkage of evidence to health outcome

#### Net Effect of Intervention

##### Substantial:

- More than a small relative impact on a frequent condition with a substantial burden of suffering, or
- A large impact on an infrequent condition with a significant impact on the individual patient level

##### Moderate:

- A small relative impact on a frequent condition with a substantial burden of suffering, or
- A moderate impact on an infrequent condition with a significant impact on the individual patient level

##### Small:

- A negligible relative impact on a frequent condition with a substantial burden of suffering, or
- A small impact on an infrequent condition with a significant impact on the individual patient level

##### Zero or Negative:

- Negative impact on patients, or
- No relative impact on either a frequent condition with a substantial burden of suffering, or
- An infrequent condition with a significant impact on the individual patient level

The evidence rating system used in the American College of Cardiology/American Heart Association (ACC/AHA) Practice Guidelines on the Evaluation and Management of Heart Failure (HF) are included below. As this is used by ACC/AHA guidelines, this format is included in the recommendations to assist in the application of the recommendations to clinical practice.

#### Level of Evidence

A: Data is derived from multiple randomized clinical trials.

B: Data is derived from a single randomized trial or nonrandomized studies.

C: Consensus opinion of experts is the primary source of recommendation.

## METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses  
Systematic Review with Evidence Tables

## DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

## METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

## DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

- Recommendations were based on evidence published in the medical literature. Critical literature review focused on pharmacologic management of heart failure (HF). The annotations that include discussion on medical history, physical examination, diagnosis and evaluation, nonpharmacologic intervention, management of concomitant cardiac conditions, and treatment of underlying causes were based on consensus and did not undergo critical literature review. Where evidence was not available, expert opinion of the medical advisory panel was used.
- Since the publication of the 1997 guideline document, major advances in the treatment of patients with HF have been published and were included in the 2001 update. Sections were added that discussed the positive outcomes associated with the use of beta-adrenergic blockers and the use of an aldosterone antagonist in specific patients with HF. A section was also added to present the evidence and considerations in using alternative afterload reduction in patients who cannot tolerate an angiotensin-converting enzyme inhibitor. Changes from the 2001 HF guideline consist of the inclusion of recommendations from the American College of Cardiology/American Heart Association (ACC/AHA) Practice Guidelines for the Evaluation and Management of HF published in 2001.

## RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

The rating scale used for this document was based on the evidence rating of the U.S. Preventive Services Task Force.

A: A strong recommendation that the intervention is always indicated and acceptable

B: A recommendation that the intervention may be useful/effective

C: A recommendation that the intervention be considered

D: A recommendation that an intervention may be considered not useful/effective, or may be harmful

I : Insufficient evidence to recommend for or against; clinical judgment should be used

The evidence rating system used in the American College of Cardiology/American Heart Association (ACC/AHA) Practice Guidelines on the Evaluation and Management of HF are included below. As this is used by ACC/AHA guidelines, this format will also be included in the recommendations to assist in the application of the recommendations to clinical practice.

Class I : Conditions for which there is evidence and/or general agreement that a given procedure/therapy is useful and effective

Class II : Conditions for which there is conflicting evidence and/or a divergence of opinion about usefulness/efficacy of performing the procedure/therapy

Class II a: Weight of evidence/opinion is in favor of usefulness/efficacy

Class II b: Usefulness/efficacy is less well established by evidence/opinion

Class III : Conditions for which there is evidence and/or general agreement that a procedure/therapy is not useful/effective and in some cases may be harmful.

## COST ANALYSIS

The guideline developers reviewed published cost analyses.

## METHOD OF GUIDELINE VALIDATION

Peer Review

## DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The draft guideline was sent to experts in the field of cardiology for review. After the cardiologist reviewers' comments were considered and incorporated into the document where appropriate, the draft was then circulated to practicing clinicians (primarily cardiologists and primary care providers) for input on clarity and applicability.

A draft of the guideline was sent to Chiefs of Pharmacy, Veterans Integrated Service Network (VISN) Formulary Leaders and co-chairs, Veterans Integrated Service Network Directors, Director of Performance Management, Consolidated Mail Outpatient Pharmacy (CMOP) Directors, Clinical Managers and the National Advisory Council for the Adoption, Development and Implementation of Clinical Practice Guidelines for peer review.

## RECOMMENDATIONS

### MAJOR RECOMMENDATIONS

The recommendations for the pharmacologic management of chronic heart failure are organized into 1 major algorithm. The algorithm, the objectives and annotations that accompany it, and the evidence supporting the recommendations are presented below. The quality of evidence (I, II-1, II-2, II-3, III), overall quality (good, fair, poor), net effect of intervention (substantial, moderate, small, zero or negative), and strength of recommendation grading (A-D, I) are defined at the end of the "Major Recommendations" field. In addition, the evidence rating system used in the American College of Cardiology/American Heart Association (ACC/AHA) Practice Guidelines on the Evaluation and Management of Heart Failure (HF), including the strength of recommendation grading (Class I, II, IIa, IIb, III) and level of evidence (A-C) are included at the end of the "Major Recommendations" field.

Note: A list of abbreviations is provided at the end of the "Major Recommendations" field.

### Algorithm: Pharmacologic Management of Patients with Heart Failure

#### A. Assess Medical History and Physical Examination in a Patient at Risk for or Suspected of Having Heart Failure (HF)

##### Objective

To identify patient factors associated with HF

##### Annotation

Approximately 4,600,000 of the U.S. population have heart failure (HF), with 550,000 new cases each year. The prevalence of HF rises with age. There is a 5 to 10% annual fatality rate in patients with mild symptoms and up to 30 to 40% in patients with advanced disease. The 5-year mortality rate is approximately 50%. Recent analyses of the last 50 years have shown that the incidence of HF is decreasing among women, although this does not appear to be occurring among men. Survival rates among both men and women have improved with a decrease in death risk of 12% per decade. Heart failure is the leading cause of hospitalization in patients over 65 years of age. It has been estimated that \$20 to 40 billion are spent for HF annually in the U.S. alone.

The leading cause of HF due to left ventricular systolic dysfunction is coronary artery disease. Nonischemic causes include hypertension (HTN), valvular heart disease, thyroid disease, myocarditis, and alcohol consumption.

1. Medical history
  - a. Prior myocardial infarction (MI) or coronary artery disease
  - b. Long standing HTN (75% of patients with HF have antecedent HTN)
  - c. Valvular heart disease
  - d. Diabetes
  - e. Peripheral vascular disease
  - f. Hypercholesterolemia

- g. Rheumatic fever
  - h. Chest irradiation
  - i. Exposure to antineoplastic agents (e.g., anthracyclines, trastuzumab)
  - j. Alcohol and illicit drug use
  - k. Exposure to sexually transmitted diseases
  - l. Family history of atherosclerotic disease, cardiomyopathy, sudden death, conduction system disease, and skeletal myopathies
2. Patient presentation: Patients with left ventricular (LV) dysfunction generally present in one of the following manners:
    - a. Decreased exercise tolerance
    - b. Fluid retention
    - c. Cardiac enlargement or dysfunction noted during evaluation for a condition other than HF
  3. Patient symptoms of HF: Most patients will present with complaints of exercise intolerance due to dyspnea and/or fatigue. However, no symptom is sufficiently sensitive or specific for the diagnosis of HF to allow ruling in or out disease. Patients with at least one of the following symptoms are at somewhat higher likelihood of having HF. Patients can have HF and have no symptoms of the disease.
    - a. Shortness of breath (SOB)
    - b. Fatigue
    - c. Orthopnea
    - d. Paroxysmal nocturnal dyspnea (PND)
    - e. Dyspnea on exertion (DOE)
    - f. Cough
    - g. Edema
    - h. Weight gain (anorexia may be seen in advanced HF)
  4. Physical examination findings of HF: No single finding is sufficiently sensitive or specific for use alone in the diagnosis of HF. However, patients with at least one of the following signs are more likely to have HF. Patients can have HF and no signs of the condition.
    - a. Tachycardia
    - b. Increasing weight
    - c. Jugular venous distention (JVD) or hepatojugular reflux
    - d. Presence of S<sub>3</sub> (third heart sound)
    - e. Laterally displaced apical impulse
    - f. Pulmonary crackles or wheezes
    - g. Hepatomegaly
    - h. Peripheral edema

## B. Diagnose and Evaluate Patient Suspected of Having HF

### Objectives

1. To distinguish between the diagnosis of HF and other conditions, such as pulmonary, hepatic, renal, hematopoietic diseases that can produce symptoms or signs suggestive of HF

2. To distinguish systolic from diastolic dysfunction
3. To evaluate the patient's functional status

#### Annotation

Signs and symptoms of HF are nonspecific and must be distinguished from those of other conditions such as pulmonary disease, liver failure, and/or nephrotic syndrome. Heart failure due to myocardial muscle dysfunction may be characterized by systolic dysfunction, diastolic dysfunction, or both. Systolic dysfunction is generally defined as a left ventricular ejection fraction (LVEF) of <40%. Patients with diastolic dysfunction often have impaired ventricular relaxation and distensibility resulting in increased ventricular filling pressure (LVEDP). The ejection fraction in these patients may be normal or increased.

#### Recommended Tests to Assist in the Diagnosis of HF

1. Analysis of venous blood sample for creatinine (Cr), blood urea nitrogen (BUN), serum electrolytes including calcium and magnesium, urinalysis, complete blood count, fasting lipid profile, liver function tests, thyroid stimulating hormone (TSH); consider serum iron and saturation to exclude hemochromatosis
2. Electrocardiogram to assess for prior MI, voltage criteria suggestive of left ventricular hypertrophy (LVH), cardiac rhythm
3. Chest radiography to identify signs of volume overload (pleural effusion, pulmonary edema, cardiomegaly) or pulmonary disease
4. All patients with HF should have an evaluation of left ventricular function.
  - a. Before a diagnosis of HF due to diastolic dysfunction can be made, other potential causes of HF with preserved LV systolic function should be ruled out (e.g., valvular regurgitation or high-output states such as anemia or pregnancy).
  - b. A diagnosis of HF due to systolic dysfunction can be made by a 2-dimensional echocardiogram with Doppler flow studies. Testing by this method will help determine if the cause is pericardial, valvular, or myocardial. If myocardial, patients with a LVEF of <40% are classified as having systolic dysfunction. Up to 40% of patients with a clinical diagnosis of HF have normal LVEF and no evidence of valvular disease. Most of these patients will have LV diastolic dysfunction.
  - c. Other tests (e.g., radionuclide ventriculography) may be used to determine left ventricular systolic function, non-invasively. Left ventriculography (cardiac catheterization) may be indicated in selected patients to assess LV function, coronary circulation, etc. Cardiology consultation can be useful in determining the need for cardiac catheterization.
  - d. The utility of measuring brain natriuretic peptide (BNP) levels has not been clearly defined although it may be useful in the diagnosis of congestive HF. It has also been used as an indicator of morbidity and mortality in patients with HF and in the acute care setting to distinguish between dyspnea from HF vs. other etiologies.

- e. First-degree relatives of patients with idiopathic dilated cardiomyopathy may be considered for an echocardiogram and electrocardiogram.

## Classification of HF

Different classification systems help characterize HF based on cardiac cycle (systolic, diastolic, or both), and/or ventricular involvement (right, left, or both). The American College of Cardiology/American Heart Association (ACC/AHA) Task Force on Practice Guidelines recently published recommendations for staging patients with HF based on the progression of disease (refer to Table 1 titled "ACC/AHA Guidelines for the Evaluation and Management of HF" in the original guideline document).

It is the intent of the ACC/AHA recommendations to be used in conjunction with the New York Heart Association (NYHA) functional classification that estimates the severity of disease based on patient symptoms (refer to Table 2 titled "NYHA Functional Classification and Objective Assessment of HF" in the original guideline document).

## C. Nonpharmacologic Interventions, Management of Concomitant Cardiac Conditions and Risk Factors, and Treatment of Underlying Causes

### Objective

To provide general interventions to be recommended in patients at risk for developing HF or who have a diagnosis of HF

### Annotation

Basic assessment should attempt to identify the etiology of the HF (e.g., ischemic heart disease, hypertension, thyroid dysfunction, valvular heart disease, brady- and tachyarrhythmias, cardiomyopathies, infiltrative diseases or hemochromatosis), and factors that may aggravate or precipitate HF (e.g., anemia, infections, obesity, or excessive salt intake).

## General Recommendations for HF Stages A-D

1. Control risk factors
  - a. Control HTN (refer to [http://www.oqp.med.va.gov/cpg/HTN04/HTN\\_base.htm](http://www.oqp.med.va.gov/cpg/HTN04/HTN_base.htm), for the clinical practice guideline on the management of hypertension and other related documents).
  - b. Treat hyperlipidemia (refer to [http://www.oqp.med.va.gov/cpg/DL/DL\\_base.htm](http://www.oqp.med.va.gov/cpg/DL/DL_base.htm), for the clinical practice guideline on the management of dyslipidemia and other related documents).
  - c. Encourage smoking cessation (refer to [http://www.oqp.med.va.gov/cpg/TUC3/TUC\\_Base.htm](http://www.oqp.med.va.gov/cpg/TUC3/TUC_Base.htm) for the clinical practice guideline on tobacco use cessation).

- d. Discourage alcohol consumption and illicit drug use.
  - e. Use of an angiotensin-converting enzyme inhibitor (ACEI) in patients with a history of coronary artery disease, peripheral vascular disease, or stroke; or diabetes mellitus (DM) plus at least one additional cardiovascular risk factor (e.g., HTN, increased total cholesterol [ $>200$  mg/dl], low high-density lipoprotein [HDL] cholesterol [ $\leq 35$  mg/dl], cigarette smoking, documented microalbuminuria).
  - f. Control ventricular rate in patients with supraventricular tachyarrhythmias.
  - g. Treat thyroid disorders.
  - h. Treat DM (refer to [http://www.oqp.med.va.gov/cpg/DM/DM\\_base.htm](http://www.oqp.med.va.gov/cpg/DM/DM_base.htm), for the clinical practice guideline on the management of diabetes and other related documents).
  - i. Manage atherosclerotic disease (refer to [http://www.oqp.med.va.gov/cpg/IHD/IHD\\_base.htm](http://www.oqp.med.va.gov/cpg/IHD/IHD_base.htm) for the clinical practice guideline on the management of ischemic heart disease and stroke).
2. To maintain fluid balance
    - a. Restrict daily sodium intake to 2 to 3 grams per day (1 gram sodium = 2.5 grams salt).
    - b. Daily weight measurements to assess for fluid retention
    - c. Fluid restriction is generally needed only to correct a clinically important hyponatremia rather than being a generalized treatment for HF; however, high fluid intake (e.g.,  $>3$  liters per day) should be discouraged.
  3. Weight loss if body mass index  $\geq 30\text{kg/m}^2$  (obesity) after adjustment for fluid retention.
  4. Moderate exercise (in conjunction with drug therapy) to improve physical conditioning in patients with stable HF, Stage C. Exercise training programs have been used in trials evaluating the effects of physical conditioning on symptoms, exercise tolerance, safety, and quality of life in patients with HF. Patients should be referred to a specialist if the clinician is not comfortable designing an exercise program for the patient with HF.
  5. Recommendations in selected patients
    - a. In patients with HF due to systolic dysfunction and atrial fibrillation requiring rate control, a beta-adrenergic blocker is preferred due to its favorable effect on patients with HF (in patients that are hemodynamically and otherwise stable). Digoxin is also commonly used. Some patients may require combination therapy with digoxin and a beta-adrenergic blocker. If additional rate control is needed, referral should be made to a cardiologist with expertise in electrophysiology. Patients with atrial fibrillation and diastolic dysfunction should be treated with verapamil or diltiazem, or a beta-adrenergic blocker to control the ventricular rate.
    - b. Warfarin anticoagulation (with a target international normalized ratio [INR] of 2.0 to 3.0) is recommended in patients with HF

and atrial fibrillation or previous systemic or pulmonary thromboembolism. The routine use of warfarin anticoagulation for HF has not been confirmed by controlled clinical trials and the benefit of warfarin in patients with HF and a cardiac thrombus has not been established. It is anticipated that the Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) trial, which is a randomized comparison of warfarin, aspirin, and clopidogrel in patients with HF, will provide guidance on the use of these agents in this patient population. Arterial thromboembolism may occur in patients with HF due to systolic dysfunction as a result of the low cardiac output and poor contractility. There are no clinical trials designed to evaluate the efficacy of warfarin anticoagulation among patients with systolic dysfunction alone. Secondary data analysis supports warfarin use in these patients. Analysis of cohorts in the Studies of Left Ventricular Dysfunction (SOLVD) who received warfarin, compared to those who did not, suggests a 25% risk reduction in all-cause mortality. However, a post-hoc analysis of a single study is not evidence enough to recommend anticoagulation in patients with systolic dysfunction. Patients with contraindications to warfarin (e.g., increased risk of bleeding, difficulty adhering to the medication regimen or regular INR monitoring, current alcohol abuse, or falls) should receive aspirin unless contraindicated.

- c. Reinstate sinus rhythm by chemical or electrical cardioversion in patients with acute atrial fibrillation where indicated to improve functional status. Patients should receive adequate treatment of HF prior to attempt at cardioversion.
- d. Consider coronary revascularization in patients with angina or anginal equivalents or known viable myocardium with known coronary artery disease.
- e. Consultation with cardiology in patients with HF and valvular heart disease.
- f. If cardiac amyloidosis is known or suspected from echocardiography or clinical grounds, further work-up and referral to a cardiologist is warranted for appropriate treatment.
- g. Patients with systolic HF and concomitant HTN should be maximized on therapy with agents such as diuretics, ACEIs, and beta-adrenergic blockers, or beta-adrenergic blockers and nitrates in patients with concomitant angina, before adding other agents. However, in patients who are not adequately controlled on these agents, treatment with a long-acting dihydropyridine (felodipine or amlodipine) may be considered based on the following information.

The negative inotropic properties of the calcium channel blockers (CCBs) may cause deleterious effects in patients with HF due to systolic dysfunction. Studies have looked at the use of the long-acting dihydropyridines, felodipine and amlodipine, in patients with systolic dysfunction. Note that neither amlodipine nor felodipine have approval by the Food and Drug Administration for use in patients with HF and should be used with caution in patients with this diagnosis.

The Prospective Randomized Amlodipine Survival Evaluation (PRAISE) evaluated patients with New York Heart Association (NYHA) class IIIB or IV with a LVEF of <30% who remained symptomatic despite treatment with digoxin, diuretics, and an ACEI. There were 571 patients who received amlodipine up to 10mg daily (qd) compared to 582 patients on placebo. The average follow-up was 13.8 months (range 6 to 33). There was no significant difference in the primary endpoint between groups which was the combined risk of death and major cardiovascular hospitalizations. There was a trend toward amlodipine to decrease all-cause mortality ( $p = 0.07$ ). Subgroup analysis showed that amlodipine significantly decreased the risk of death from all causes in patients with HF due to nonischemic dilated cardiomyopathy, without a difference in patients with ischemic dilated cardiomyopathy. This result was not considered a priori endpoint. The survival benefit of amlodipine in patients with nonischemic dilated cardiomyopathy found in the original PRAISE trial was not confirmed in PRAISE-2.

The third Vasodilator Heart Failure Trial (V-HeFT III) included patients with NYHA class II or III HF with a LVEF of 18 to 42% who remained symptomatic despite treatment with digoxin, diuretics, and an ACEI. There were 224 patients who received felodipine at a maximum dose of 5 mg twice a day (bid) compared to 226 patients on placebo. The average follow-up was 18 months (range 3 to 39). The primary endpoint of the study was the effect of treatment on exercise tolerance. There was no significant difference between groups in death from all causes, worsening HF, or number of hospitalizations. This study was not sufficiently powered to demonstrate that felodipine did not alter mortality, however. Exercise tolerance and quality of life significantly improved with felodipine at 27 months.

Clinical experts have stated that only trials with amlodipine and felodipine have provided long-term safety data in patients with HF. The evidence with amlodipine suggests that this agent does not adversely affect survival in patients with systolic HF. Felodipine or amlodipine may be considered for the treatment of hypertension and/or angina in patients with HF due to systolic dysfunction. The Pharmacy Benefits Management-Medical Advisory Panel (PBM-MAP) Criteria for Use of the Long-Acting Dihydropyridine Calcium Antagonists can be found at <http://www.oqp.med.va.gov/cpg/cpg.htm>.

#### 6. Medications to avoid

- a. Anti-arrhythmic agents, other than beta-adrenergic blockers, are not recommended to suppress asymptomatic ventricular arrhythmia or ectopy. Class I anti-arrhythmic agents have been shown to increase the risk of sudden death in patients with HF. Of the class III agents, treatment with amiodarone or dofetilide does not appear to increase the risk of death in patients with

HF. Patients with ventricular arrhythmias should be referred to a cardiologist with expertise in electrophysiology for individualized treatment.

- b. Most CCBs (except felodipine and amlodipine) should not be used in patients with systolic dysfunction (refer to 5g above).
- c. Non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided; alternative anti-inflammatory agents may be used (e.g., non-acetylated salicylates).
- d. Antineoplastic agents such as anthracyclines or trastuzumab may lead to the development of HF and should be avoided, if possible.
- e. Conventional wisdom has been that digoxin and CCBs should be avoided in patients with amyloid cardiomyopathy. However, this point is controversial and supported by only weak published evidence. Several case reports suggest a sensitivity to digoxin; however, one prospective autopsy study found no association. Digoxin can be useful in controlling rapid ventricular response to atrial fibrillation and might be useful, especially in early stages of systolic dysfunction caused by amyloid cardiomyopathy. The data supporting a CCB sensitivity is based on case reports for nifedipine and verapamil. Both these drugs can exacerbate chronic systolic dysfunction independent of etiology. The guideline developers can find no case reports of other CCBs to suggest sensitivity to them. The following recommendations are based on review of available evidence:
  - Avoid verapamil, diltiazem, and nifedipine in systolic dysfunction of all etiologies.
  - If digoxin is necessary in a patient with known or suspected amyloid cardiomyopathy (e.g., to control ventricular response to atrial fibrillation), it should be used very cautiously with careful monitoring for evidence of cardiac toxicity.
  - Use digoxin in severe cases of known or suspected amyloid cardiomyopathy only in close consultation with a cardiologist and after carefully weighing the potential risks and benefits.
  - Use felodipine or amlodipine only according to prescribing guidelines. Monitor patients with known or suspected amyloid cardiomyopathy very closely when using any CCB.
  - Consider using other agents for diastolic dysfunction before resorting to a CCB in patients with known or suspected amyloid cardiomyopathy.

#### 7. Additional recommendations

- a. Unless contraindicated, influenza vaccination should be offered every fall.
- b. Pneumococcal immunizations should be provided at diagnosis if not previously vaccinated. If initial vaccination was at age less than 65 years, revaccinate at age 65 or 5 years after initial immunization, whichever is later.
- c. Patients and their families or caregivers should receive education on HF, dietary restrictions, drug therapy and

importance of adherence to the medication regimen, symptoms associated with worsening HF and what to do if they occur, and prognosis.

- d. Patients should be followed closely by a clinician competent in caring for patients with HF. Care of patients with HF may occur in several clinical settings including primary care, cardiology, or by multidisciplinary HF treatment teams. Regardless of the setting in which patients with HF are cared for, the clinician is encouraged to follow these and other HF guidelines and to use clinical judgment of when to refer to a specialist. This will depend on the skill and experience of managing patients with HF, and also the resources available to the practitioner. Interdisciplinary HF disease management clinics have improved patient outcomes including fewer HF events, achievement of higher ACEI and beta-adrenergic blocker use and doses, and lower mortality.

#### D. Pharmacologic Management of HF Due to Diastolic Dysfunction

##### Objective

To discuss pharmacologic recommendations for patients with HF due to diastolic dysfunction

##### Annotation

In diastolic dysfunction the systolic function of the left ventricle is preserved. The defect of ventricular function lies in the reduced LV compliance and difficulty in passive filling. Increased LVEDP can result in pulmonary congestion indistinguishable clinically from LV systolic dysfunction.

Compared to HF due to systolic dysfunction, there is a paucity of data from randomized trials about the pharmacologic management of patients with diastolic dysfunction. Since questions remain regarding the optimal treatment of patients with diastolic dysfunction, it is recommended that these patients be treated in conjunction with a cardiologist.

General principles of lowering blood pressure, treating myocardial ischemia, slowing atrioventricular (AV) conduction, controlling central blood volume, and providing anticoagulation for patients with atrial fibrillation apply to these patients as well as to patients with systolic dysfunction.

The main goal of therapy is to improve symptoms by lowering the filling pressures of the left ventricle without significantly reducing cardiac output. Agents that decrease heart rate can be helpful by increasing diastolic filling time.

##### Pharmacologic recommendations of HF due to diastolic dysfunction:

##### Strength of Recommendation and Evidence Rating

Grade A (always indicated and acceptable):

- Control blood pressure. (Overall Quality: Good; Net Effect: Substantial; ACC/AHA Recommendation: Class I; Evidence Level: A) (Hunt et al., 2001)

Grade B (may be useful/effective):

- Judicious use of diuretics in patients with symptoms of volume overload (Overall Quality: Poor; Net Effect: Moderate; ACC/AHA Recommendations: Class I; Evidence Level: C) (Lenihan et al., 1995; Goldsmith & Dick, 1993; Bonow & Udelson, 1992; Vasan, Benjamin, & Levy, 1996)
- Use drugs that control ventricular rate in patients with atrial fibrillation. (Overall Quality: Poor; Net Effect: Moderate; ACC/AHA Recommendations: Class I; Evidence Level: C) (Hunt et al., 2001)

Grade C (may be considered):

- Digoxin improves symptoms and reduces hospitalizations in patients with diastolic dysfunction in the absence of atrial fibrillation. (Overall Quality: Poor; Net Effect: Moderate; ACC/AHA Recommendation: Class IIb; Evidence Level: C) (Massie & Abdalla, 1998; "The effect of digoxin," 1997)
- Use beta-adrenergic blockers, CCBs, ACEI, angiotensin II receptor antagonists (AIIIRAs) in patients with controlled blood pressure who continue to have symptoms. (Overall Quality: Poor; Net Effect: Small; ACC/AHA Recommendation: Class IIb; Evidence Level: C) (Hunt et al., 2001; Goldsmith & Dick, 1993; Bonow & Udelson, 1992; Weinberger, 1999; Setaro et al. 1990; Dahlof, Pennert, & Hansson, 1992; Gottdiener et al., 1997; Warner et al., 1999)
- Use nitrates in patients with diastolic dysfunction as a result of coronary artery disease. (Overall Quality: Poor; Net Effect: Small; ACC/AHA Recommendations: NA; Evidence Level: NA) (Lenihan et al., 1995; Goldsmith & Dick, 1993; Bonow & Udelson, 1992; Vasan, Benjamin, & Levy, 1996; Zile & Brutsaert, 2002)

Grade D (may not be useful/effective; possibly harmful):

- None

Grade I (insufficient evidence to recommend for or against):

- None

#### E. Interventions in Patients With Asymptomatic Left Ventricular Systolic Dysfunction

Objective

To provide recommendations for patients with asymptomatic left ventricular systolic dysfunction (Stage B)

#### Annotation

The management goals for patients with asymptomatic systolic dysfunction are to initiate therapy in an effort to prevent the development of HF. These recommendations are divided into the following patient groups.

#### Patients With an Acute, Recent, or History of MI

Prescribing an ACEI in patients with an acute or recent MI and evidence of left ventricular systolic dysfunction may reduce mortality and slow the progression to symptomatic heart failure. In the Survival and Ventricular Enlargement (SAVE), Acute Infarction Ramipril Efficacy (AIRE), and Trandolapril Cardiac Evaluation (TRACE) trials, patients with a recent MI and evidence of HF experienced a significant decrease in all-cause mortality and risk of developing severe heart failure when treated with an ACEI compared to placebo. Treatment with an ACEI in patients recently recovered from an MI can decrease the risk of reinfarction and death in patients with evidence of HF at the time of the infarction. Patients with a history of MI without LVEF may also benefit from treatment with a ACEI.

The use of a beta-adrenergic blocker in patients with asymptomatic left ventricular systolic dysfunction post-MI reduces the risk of cardiovascular morbidity and mortality. In the Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN) trial that randomized 1,959 patients with a LVEF  $\leq 40\%$  post-MI to carvedilol or placebo, there was not a statistically significant difference in the primary endpoint of all-cause mortality or hospital admission for cardiovascular problems (originally a prespecified secondary endpoint). The original primary endpoint of all-cause mortality (changed to co-primary endpoint due to inadequate sample size and power) was lower (but not statistically significant based on  $\alpha=0.005$  for all-cause mortality alone) in patients on carvedilol compared to placebo (hazard ratio 0.77 [0.60-0.98],  $P=0.03$ ). Although the results of this study did not achieve statistical significance (thought to be due to trial design), the endpoints were lower in patients treated with carvedilol. Taking this into account with results of other trials, there still appears to be a benefit of using a beta-adrenergic blocker in patients with asymptomatic left ventricular systolic dysfunction post-MI.

Combination therapy with a beta-adrenergic blocker and an ACEI may also be beneficial in patients with left ventricular systolic dysfunction post-MI.

Future results of clinical trials should provide data as to the potential benefit of the AIIRAs in patients with a recent MI.

#### Patients With Chronic Asymptomatic Left Ventricular Dysfunction

In the Studies of Left Ventricular Dysfunction (SOLVD) Prevention trial, patients with asymptomatic left ventricular dysfunction treated with an ACEI experienced a significant reduction in the combined risk of death and

hospitalization for HF by 20% compared to placebo. However, there was no significant decrease in all-cause mortality alone in the ACEI group. The benefit of an ACEI in men compared to women with HF was recently evaluated. According to a subgroup analysis of trials including treatment of patients with asymptomatic LV dysfunction, there did not appear to be a clear benefit of ACEI in women, with a relative risk of 0.96 (95% CI 0.75-1.22). It was concluded that further investigation is warranted before making a definitive recommendation on the use of ACEIs in women with asymptomatic left ventricular dysfunction. While the benefit, to the extent that one exists, remains to be quantified, an ACEI should still be considered standard therapy given the current level of data overall.

Although the benefit of beta-adrenergic blockers in patients with asymptomatic HF (not in the post-MI setting) has not been critically evaluated, current recommendations include use of a beta-adrenergic blocker in this patient population.

Digoxin is currently recommended in patients with symptomatic HF to improve clinical status and decrease the risk of hospitalization due to HF (refer to Annotation L). Since there is not a significant reduction in disease progression or mortality, digoxin is not recommended in patients with asymptomatic left ventricular dysfunction.

#### Pharmacologic recommendations for patients with asymptomatic systolic dysfunction:

##### Strength of Recommendation and Evidence Rating

##### Grade A (always indicated and acceptable):

- ACEI in patients with acute, recent, or history of MI, regardless of LVEF (Overall Quality: Good; Net Effect: Substantial; ACC/AHA Recommendations: Class I; Evidence Level: A) (Hunt et al., 2001; ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group, 1995; "Six-months effects," 1996; Pfeffer et al., 1992; "Effect of ramipril on mortality," 1993; Hall, Murray, & Ball, 1997; Kober et al., 1995; Yusuf et al., 2000)
- ACEI in patients with reduced LVEF, whether or not history of MI (Overall Quality: Good; Net Effect: Substantial; ACC/AHA Recommendations: Class I; Evidence Level: B) (Hunt et al., 2001; "Effect of enalapril," 1992)
- Beta-adrenergic blocker in patients with acute, recent, or history of MI, regardless of LVEF (Overall Quality: Good; Net Effect: Substantial; ACC/AHA Recommendations: Class I; Evidence Level: A) (Hunt et al., 2001; Gottlieb, McCarter, & Vogel, 1998; "Timolol-induced reduction," 1981; "A randomized trial of propranolol," 1982; Chadda et al., 1986; Dargie, 2001; Vantrimpont et al., 1997)
- Beta-adrenergic blocker in patients with reduced LVEF, whether or not history of MI (Overall Quality: Fair; Net Effect: Substantial; ACC/AHA Recommendations: Class I; Evidence Level: B) (Hunt et al., 2001, "Timolol-induced reduction," 1981; "A randomized trial of

propranolol," 1982; Chadda et al., 1986; Dargie, 2001; Vantrimpont et al., 1997)

Grade B (may be useful/ effective):

- None

Grade C (may be considered):

- None

Grade D (may not be useful/effective; possibly harmful):

- Digoxin in patients with asymptomatic left ventricular dysfunction in sinus rhythm (Overall Quality: Poor; Net Effect: Zero; ACC/AHA Recommendations: Class III; Evidence Level: C) (Hunt et al., 2001; The effect of digoxin," 1997)

Grade I (insufficient evidence to recommend for or against):

- None

#### F. Systolic Dysfunction and Assessment for Symptoms of Volume Overload

##### Objective

To provide recommendations for initial therapy in patients with a diagnosis of systolic HF who exhibit symptoms of volume overload

##### Annotation

The goals of treating patients with HF due to systolic dysfunction are to improve the patient's symptoms and quality of life and to reduce the risk of morbidity and mortality by slowing the progression of disease. Patient's symptoms are often related to volume overload.

Symptoms of volume overload include ankle swelling, weight gain, fatigue, orthopnea, PND, DOE, SOB at rest, and nocturnal cough. The signs of volume overload are pulmonary crackles, third heart sound cardiomegaly, JVD, hepatojugular reflux, hepatomegaly, ascites, dependent edema (presacral, flank, lower extremity), tachypnea, tachycardia, and pulmonary edema.

Chest radiography is useful to identify signs of volume overload (pleural effusion, pulmonary edema, cardiomegaly).

A diuretic is recommended in patients with HF who exhibit signs or symptoms of volume overload. (refer to Annotation G)

#### G. Diuretic Therapy

## Objective

To provide recommendations for the appropriate use of diuretics in patients with a diagnosis of systolic HF (for a discussion on the use of aldosterone antagonists in HF, refer to Annotation M)

## Annotation

Diuretics act by inhibiting sodium or chloride reabsorption in the renal tubules. The loop diuretics exert their effects more proximally and are therefore the most potent of the diuretics. The diuretics primarily differ in their duration of action (e.g., furosemide 6 hours, hydrochlorothiazide 6 to 12 hours, metolazone 12 to 24 hours). As HF progresses, a delay in absorption may be a contributing factor to the need for increasing diuretic doses in some patients.

There have been no long-term controlled clinical trials evaluating the effectiveness of loop or thiazide diuretic therapy in patients with HF. Short-term and intermediate length studies have demonstrated that diuretics can decrease the signs and symptoms of fluid retention and improve cardiac conduction and exercise tolerance. The majority of patients enrolled in long-term trials demonstrating a decreased morbidity or mortality with ACEI or beta-adrenergic blocker therapy were also receiving a diuretic.

Some patients with HF may experience a recurrence of symptoms if diuretic therapy is withdrawn. In one trial the risk of requiring reinstitution of diuretic therapy was 36% in patients in the withdrawal group compared with controls. A LVEF  $\leq 27\%$ , diuretic dose greater than 40 mg of furosemide daily, or a history of HTN were independent risk factors for early reinstitution of diuretic therapy.

Patients with HF may have symptoms that interfere with their daily activities and, therefore, impact on their quality of life. A diuretic should be used for preload reduction in patients with HF and current or previous signs or symptoms of volume overload (e.g., orthopnea, PND, DOE, or edema). Patients with symptoms of fluid overload benefit from treatment with a diuretic in conjunction with an ACEI and beta-adrenergic blocker, and possibly digoxin.

Loop diuretics are most commonly used for patients with HF and volume overload. They are effective in patients with renal insufficiency or creatinine clearance (CrCl)  $< 30$  mL/min, whereas the effectiveness of thiazides are diminished in patients with CrCl  $< 30$  mL/min. Edema resistant to large doses of loop diuretics may intermittently require combined diuretic therapy (e.g., adding metolazone or thiazide at low doses two to three times per week or more frequently if needed, one hour prior to a loop diuretic), or intravenous diuretics. The use of combination diuretics increases the risk of electrolyte imbalances and overdiuresis leading to prerenal azotemia. Therefore, combination diuretic therapy requires close monitoring.

Monitoring parameters with diuretics include the following:

1. Weight: (initially 1- to 2-pound weight loss per day until "ideal weight" achieved); weight loss may be greater during the first few days when significant edema is present; obtain daily weights
2. Signs or symptoms of volume depletion: weakness, dizziness, decreased urine output, symptomatic hypotension, orthostatic hypotension
3. Serum potassium (K +), BUN, or Cr (and serum BUN/Cr ratio); consider magnesium (especially if high doses diuretic used), sodium, calcium, bicarbonate, uric acid, glucose as indicated. Use of an ACEI (or AIIRA) and/or spironolactone may offset potential diuretic-induced hypokalemia, minimizing the need for potassium or potassium-sparing diuretics.
4. Diuretic dosage may require adjustment if hypotension or decrease in renal function occurs. Avoid excessive diuresis, which could also limit ACEI dosage due to hypotension or renal dysfunction.

See Table 3 titled "Diuretic Therapy" in the original guideline document.

Pharmacologic recommendations for diuretic therapy in patients with HF:

Strength of Recommendation and Evidence Rating

Grade A (always indicated and acceptable):

- Use loop diuretic in patients with evidence of fluid overload. (Overall Quality: Fair; Net Effect: Moderate; ACC/AHA Recommendations: Class I; Evidence Level: A) (Hunt et al., 2001; Patterson et al., 1994; Wilson et al., 1981; Parker, 1993; Richardson et al., 1987; Cleland, Swedberg, & Poole-Wilson, 1998)

Grade B (may be useful/effective):

- Use combination of loop diuretic and either thiazide or metolazone in patients refractory to loop diuretic. (Overall Quality: Fair; Net Effect: Moderate; ACC/AHA Recommendations: NA; Evidence Level: NA) (Hunt et al., 2001; Young et al., 1998; Agency for Health Care Policy and Research (AHCPR), 1994; Ellison, 1991; Brater, 1994; Channer et al., 1994; Oster, Epstein, & Smoler, 1983; Sica & Gehr, 1996)

Grade C (may be considered):

- None

Grade D (may not be useful/effective; possibly harmful):

- None

Grade I (insufficient evidence to recommend for or against):

- None

## H. Angiotensin-Converting Enzyme Inhibitors

### Objective

To provide recommendations for the appropriate use of ACEIs in patients with a diagnosis of systolic HF.

### Annotation

Angiotensin-converting enzyme (ACE) is responsible for converting angiotensin I to angiotensin II. Angiotensin II is a potent vasoconstrictor and it stimulates aldosterone secretion, which leads to increased sodium and water retention. By inhibiting this enzyme, ACEIs ultimately reduce the vasoconstriction associated with angiotensin II and decrease the sodium and water retention associated with aldosterone. ACE is structurally similar to kininase II, so it may also inhibit the breakdown of bradykinin, a vasodilator. The importance of ACE's effect on kinin-mediated prostaglandin synthesis in the management of patients with HF is not yet known, but it may be as important as angiotensin suppression.

In addition to improving HF symptoms and functional status, treatment with an ACEI has been shown to decrease the frequency of hospitalization and mortality rate.

In the Captopril-Digoxin Multicenter Trial, patients with mild to moderate HF were randomized to placebo or captopril in addition to treatment with diuretics for 6 months. Patients on captopril experienced significant improvement in exercise tolerance and decreased frequency of hospital or emergency care for worsening HF.

Patients with mild to moderate HF who received enalapril for an average of 41 months in the SOLVD Treatment Trial had a significant decrease of 16% in all-cause mortality (confidence interval [CI] 0.05 to 0.26,  $P=0.0036$ ; ARR 4.55%; NNT=22.0) and a 26% decreased risk of death or hospitalizations for HF compared to patients on placebo.

The Vasodilator Heart Failure Trial (V-HeFT) II showed that patients with mild to moderate HF who received enalapril for an average of 2.5 years experienced a significant decrease of 28% ( $P=0.016$ ) in the risk of death at 2 years compared to patients on the combination hydralazine and isosorbide dinitrate (HYD/ISDN) (ARR 5.41%; NNT=18.5).

The Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) evaluated treatment with enalapril for 6 months compared to placebo in patients with NYHA class IV HF. There was not a significant benefit in the combined risk of death and hospitalizations for HF in patients on enalapril. Treatment with enalapril significantly decreased all-cause mortality at 6 months (RR 0.40,  $P=0.002$ ; ARR 17.67%; NNT=5.7).

The possibility of racial differences in response to therapy has been seen in a subanalysis of V-HeFT and V-HeFT II, where white patients did not experience the same mortality benefit as black patients on HYD/ISDN. In V-HeFT II, white patients on an ACEI experienced a decrease in mortality compared to treatment with HYD/ISDN, whereas black patients did not. When matched cohorts of white patients were compared to black patients on an ACEI enrolled in the SOLVD Treatment Trial, white patients experienced a decreased risk for hospitalizations due to HF which was not seen in the cohort of black patients. Based on a pooled relative risk analysis, there was no evidence that mortality differed substantially with an estimate for white patients of 0.89 (95% CI 0.82-0.97) and 0.89 (85% CI 0.74-1.06) for black patients. Further trials will need to be conducted to determine if recommended therapy for HF needs to be modified based on patient demographics.

It is recommended that an ACEI should be offered to all patients with reduced left ventricular systolic dysfunction unless the patient has specific contraindications:

1. A history of angioedema or other documented hypersensitivity to an ACEI
2. Bilateral renal artery stenosis or renal artery stenosis in a solitary kidney
3. Pregnancy
4. Serum potassium >5.5 mEq/L that cannot be reduced
5. Symptomatic hypotension

Before initiating therapy, patients should first be assessed for adequate volume status. If the patient is on a potassium-sparing diuretic when an ACEI is begun, close monitoring of potassium is recommended. Alternatively, the potassium-sparing diuretic may be stopped while titrating the ACEI and re-started later, if hypokalemic, with subsequent close monitoring of potassium.

Patients at high risk of first dose hypotension (e.g., advanced age, volume depletion, diuretic use, severe left ventricular dysfunction, initial systolic blood pressure <100 mm Hg, or serum sodium <135 mEq/L) should be given a small dose (i.e., 6.25 to 12.5 mg) of a short acting ACEI (captopril) and monitored for 2 hours. Significant hypotension may signal the need for reducing the dosage of diuretics or other blood pressure lowering agents.

Patients started on an ACEI should be evaluated within 1 to 2 weeks to monitor blood pressure, serum potassium, and creatinine; more frequent monitoring may be warranted depending on the severity of the patient's condition.

Doses should initially be low and then titrated upward over several weeks to the maximum dose tolerated, with the target doses based on those used in large scale clinical trials (refer to Table 3 in the original guideline document). Despite the overwhelming evidence in favor of treating HF patients with ACEIs and that a large majority of patients are able to tolerate high doses, these agents are often underutilized, and frequently at low doses, although this may depend on the clinical setting.

There appears to be a dose response benefit as shown in the Assessment of Treatment with Lisinopril and Survival (ATLAS) study. In this study, patients with NYHA class II-IV HF on maximal doses of lisinopril (average of  $33.2 \pm 5.4$  mg daily) experienced a significant 12% decrease in the risk of death or hospitalization for any reason and 24% fewer hospitalizations for HF, compared to patients receiving lower doses (average of  $4.5 \pm 1.1$  mg daily). There was also a nonsignificant 8% lower risk of death in the high dose compared to the low dose treatment group. The authors observed that the decrease in risk with the high dose compared to the low dose group in the ATLAS study was approximately half that seen with target doses of an ACEI compared to placebo in other trials. This suggests that even patients on suboptimal doses will derive benefit, although not as great as patients receiving higher doses. This is important to realize since other factors may preclude a patient from achieving target doses. In another trial, patients on high doses of an ACEI (enalapril 20 mg/d) had a decreased risk of HF hospitalizations compared to patients on medium and lower doses (enalapril 10 mg/d and 5 mg/d, respectively). There was no difference between doses in symptoms or mortality. There was also no difference in NYHA class, LVEF, or mortality in a trial of patients on standard ( $17.9 \pm 4.3$  mg/d) compared to high ( $42 \pm 19.3$  mg/d) doses of enalapril.

Due to the strong evidence for the beneficial effects of ACEIs in patients with HF, every effort should be made to adjust the dosage before a patient is documented as intolerant. Dosage should be modified if the patient develops any of the following:

1. While creatinine often increases (usually <25%) after initiation of an ACEI, clinically significant decline in renal function (suggested by a change in serum Cr concentration of at least 0.5 mg/dL) should be investigated. Consultation with a nephrologist should be considered for persistent deteriorations in renal function that cannot be explained or corrected.
2. Hyperkalemia (potassium >5.5 mEq/L), after other causes have been excluded
3. If patient cannot tolerate ACEI due to symptomatic hypotension, consider referral to a cardiologist for assistance in titrating the ACEI dosage.
4. The cough associated with an ACEI has been described as dry, nonproductive, persistent, beginning with a tickling sensation, and often worse at night. The onset is usually within the first week of ACEI therapy and continues throughout treatment, resolving within a few days to 4 weeks after the ACEI is discontinued. The cough is not usually dose-dependent, although in some instances it may be eliminated with a reduction in dose. In addition, fosinopril may be considered in patients who experience cough on another ACEI. Since therapy with an ACEI has proven valuable, it is important to consider alternative diagnoses (e.g., asthma, chronic obstructive pulmonary disease, allergic rhinitis, upper respiratory tract infection, heart failure, gastroesophageal reflux disease) before a diagnosis of ACEI-induced cough is made. If the cough is not bothersome, the benefits of continuing the ACEI should be discussed with the patient.

Special considerations with ACEI use:

1. The dose of an ACEI needs to be individualized with special consideration to age, indication, renal function, concomitant medication, and/or diseases.
2. Prior to initiating ACEIs, obtain baseline serum potassium, Cr, and BUN; ACEIs should be used cautiously in patients with serum Cr >3 mg/dL.
3. Patients should be monitored and follow-up laboratory tests obtained within 1 to 2 weeks (or sooner if worsening renal function); patients at high risk for hypotension should be seen sooner or can be instructed on home blood pressure monitoring.
4. In patients taking diuretics, symptomatic hypotension may occur following initiation of an ACEI; if the diuretic cannot be discontinued, consider a lower starting dose of an ACEI.
5. Lower initial doses should be considered in HF patients; doses then should be titrated to maximum tolerated dose.
6. Lower doses should be administered for hemodynamically stable post-MI patients.
7. Captopril doses greater than 150 mg per day are generally not necessary and are associated with an increased risk of neutropenia or rash and should be used with caution if felt to be clinically justified.
8. For most ACEIs, the dose should be reduced in renal dysfunction.
9. Avoid concomitant use with potassium-sparing medications and NSAIDs whenever possible; use with caution with spironolactone. NSAIDs used in conjunction with an ACEI may worsen renal function and contribute to hyperkalemia (refer to Appendix B in the original guideline document for common drug interactions).
10. There is some controversy as to whether use of aspirin decreases the cardiovascular benefit of an ACEI when used concomitantly. Some of the beneficial effects of ACEIs are thought to be due to inhibiting the breakdown of bradykinin, which in turn, increases the production of vasodilatory prostaglandins. Aspirin, which blocks cyclooxygenase, may therefore interfere with the full benefit of an ACEI by inhibiting vasodilatory prostaglandin synthesis. Much of the discussion was prompted from the publication of retrospective analyses of data from large trials evaluating the benefits of treatment with an ACEI. A cohort analysis of SOLVD found that treatment with an antiplatelet agent (e.g., aspirin or dipyridamole) was associated with a reduction in all-cause mortality and a decrease in the risk of death or hospital admission for HF. In contrast, this association was not apparent in patients treated with an ACEI who were on an antiplatelet agent at baseline, and patients on an ACEI did not experience a reduction in all-cause mortality as did patients randomized to enalapril who were not on an antiplatelet agent. There was a reduction in the combined risk of death or hospital admission for HF in patients on an ACEI and antiplatelet agent. In an analysis of CONSENSUS II in patients with acute MI, those in the ACEI treatment group who were taking aspirin at baseline experienced a lower mortality benefit than patients who were on an ACEI without aspirin. It is difficult to determine the clinical significance of these results given the retrospective nature of the analyses and the potential contribution of differences in the groups at baseline. Given the benefit of aspirin in patients with coronary artery

disease, there is insufficient evidence to warrant a change in the current recommendations in patients with coronary artery disease and HF. Ongoing prospective evaluations of warfarin or antiplatelet therapy in patients with HF may provide additional information in order to determine the most appropriate therapy for patients in whom an antiplatelet agent and ACEI are indicated.

See Table 4 titled "ACE Inhibitors" in the original guideline document.

Pharmacologic recommendations for ACEIs in patients with HF:

Strength of Recommendation and Evidence Rating

Grade A (always indicated and acceptable):

- Use maximally tolerated doses of ACEIs to improve symptoms and mortality and reduce hospitalizations in patients with HF. (Overall Quality: Good; Net Effect: Substantial; ACC/AHA Recommendations: Class I; Evidence Level: A) (Hunt et al., 2001; "Consensus recommendations," 1999; "A placebo-controlled trial of captopril," 1983; Sharpe et al., 1984; Chalmers et al., 1987; Pflugfelder, et al., 1993; Gunderson et al., 1994; Erhardt et al., 1995; Lechat et al., 1993; "Comparative effects of therapy with captopril," 1988; "Effect of enalapril on survival," 1991; Cohn et al., 1991; "Effects of enalapril on mortality," 1987)
- Even lower-dose ACEIs will reduce mortality if target dosage is not tolerated. (Overall Quality: Good; Net Effect: Moderate; ACC/AHA Recommendations: NA; Evidence Level: NA) (Bungard et al., 2001; Packer et al., 1999; "Clinical outcome with enalapril," 1998)

Grade B (may be useful/effective):

- None

Grade C (may be considered):

- None

Grade D (may not be useful/effective; possibly harmful):

- None

Grade I (insufficient evidence to recommend for or against):

- None

I. Beta-Adrenergic Blockers

Objective

To provide recommendations for the appropriate use of beta-adrenergic blockers in patients with a diagnosis of systolic HF

#### Annotation

Activation of the sympathetic nervous system (SNS) is one of the proposed compensatory mechanisms to maintain circulation in the presence of left ventricular dysfunction. However, activation of the SNS can result in beta-receptor down-regulation, LVH, cardiotoxic effects, and arrhythmia. It is thought that one or more of these effects may contribute to HF progression. Therefore, using a beta-adrenergic blocker in a patient with HF due to systolic dysfunction could potentially negate some of these adverse effects on the heart. Until recently, the use of beta-adrenergic blockers has been considered contraindicated in patients with HF due to the recognized negative inotropic effects of these agents.

Numerous trials have shown the beneficial effects of beta-adrenergic blockers in reducing symptoms, hospitalization, and progression of disease in patients with HF due to systolic dysfunction. However, more recent evidence has demonstrated a significant reduction in mortality with the use of beta-adrenergic blockers in this patient population (see Table 5 of the original guideline document). The beta-adrenergic blockers that have been studied for chronic HF and have demonstrated a clear reduction in mortality include bisoprolol, carvedilol, and metoprolol. Other beta-adrenergic blockers may have similar benefit; however, definitive studies evaluating other beta-adrenergic blockers are lacking. Patients with stable HF due to systolic dysfunction, with appropriate volume control and adequate afterload reduction, should receive therapy with a beta-adrenergic blocker unless contraindicated.

One trial in patients with advanced HF did not show a statistically significant improvement in mortality as was seen in the COPENICUS trial. The Beta-Blocker Evaluation of Survival Trial (BEST) evaluated 2,708 patients with NYHA class III (92%) or IV (8%) HF and a LVEF  $\leq 35\%$  who were randomized to placebo or bucindolol (not available in the U.S.). Patients were excluded if their systolic blood pressure was  $< 80$  mm Hg or heart rate (HR)  $< 50$  bpm. According to the authors, the trial was discontinued after a mean follow-up of 2 years due to the evidence from BEST and other trials that beta-adrenergic blockers are beneficial in patients with HF. Upon termination of BEST, there was not a significant difference in the primary endpoint of mortality between the two groups of patients (adjusted  $P = 0.13$ ). The secondary endpoint of cardiovascular death was lower in patients on bucindolol ( $P = 0.04$ ). There were a decreased proportion of patients with HF-related hospitalizations ( $P < 0.001$ ) and with the combined endpoint of death or heart transplant ( $P = 0.04$ ). After subgroup analysis, there was a significant survival benefit in nonblack patients ( $P = 0.01$ ) but not in black patients ( $P = 0.27$ ). There was also a trend toward improved survival in patients with less severe HF ( $P = 0.05$  in patients with LVEF  $> 20\%$ ). The authors stated that due to the small number of patients with NYHA class IV HF, definitive conclusions could not be made in these patients.

In a subgroup analysis of MERIT-HF, 795 patients with NYHA class III or IV HF with a LVEF <25% who received placebo or metoprolol XL were compared. Similar to COPERNICUS, the mean baseline LVEF was 19.1% and the annual mortality for patients in the placebo group was 19%. Patients randomized to metoprolol XL experienced a decreased risk of total mortality (39%,  $P = 0.0086$ ), death due to worsening HF (55%,  $P = 0.015$ ), hospitalization due to worsening HF (45%,  $P < 0.0001$ ), and combined all-cause mortality or all-cause hospitalization (29%,  $P = 0.0012$ ) compared to placebo.

In another post-hoc analysis of MERIT-HF, the beneficial effects on morbidity and mortality with metoprolol XL were also seen in the subgroup of 898 women, including 183 women with stable severe HF.

The difference in response in black compared to nonblack patients in BEST is contrary to findings from a retrospective comparison of patients enrolled in the U.S. Carvedilol Heart Failure Study, where the benefit of carvedilol was not statistically significantly different between black and nonblack patients. A recent meta-analysis by the U.S. Department of Health and Human Services reported the estimate of pooled random-effects of the relative risk for mortality in black patients to be 0.67 (95% CI 0.39-1.16) compared to 0.63 (95% CI 0.52-0.77) for white patients. Results were similar for the pooled estimates from the hazard ratio analysis. The evidence report to address the potential difference in mortality of beta-adrenergic blockers depending on race concluded that black patients should derive the same benefits as white patients when treated with bisoprolol, carvedilol, or metoprolol (the results of BEST were not included in the pooled analysis).

The question of whether to use a selective beta-adrenergic blocker (e.g., bisoprolol or metoprolol) versus a non-selective agent with alpha-adrenergic blocking and antioxidant effects (e.g., carvedilol) remains controversial. Although the Carvedilol Or Metoprolol European Trial (COMET) demonstrated a statistically significant improvement in survival with carvedilol compared to immediate-release metoprolol (metoprolol tartrate), it is unknown whether there is a difference between carvedilol and immediate-release metoprolol or metoprolol XL (metoprolol succinate) when prescribed at the recommended target doses. Since metoprolol XL was not available at the time of enrollment in COMET, immediate-release metoprolol was selected as the comparator to carvedilol, at doses that were expected to result in comparable beta-blockade. Much of the discussion about the results of COMET includes the difference in target dose and effect on resting heart rate. The dose of carvedilol used in COMET achieved a similar reduction in heart rate as seen in U.S. Carvedilol (i.e., 13 beats per minute). The mean dose of immediate-release metoprolol used in COMET was less than the mean dose in the Metoprolol in Dilated Cardiomyopathy (MDC) trial (i.e., 85 vs. 108 mg/d), and resulted in less of a decrease in heart rate (i.e., 11.7 vs. 15 beats per minute). The mean dose in MERIT-HF was 159 mg/d and achieved a reduction in heart rate of 14 beats per minute. Whether these factors had an influence on the results is unknown. Very few trials with beta-adrenergic blockers that are available in the U.S. other than bisoprolol, carvedilol, or metoprolol have been published. It is therefore unknown if treatment with other beta-adrenergic blockers would provide the same benefits as seen with the agents that have demonstrated a reduction in mortality in patients with heart failure.

The majority of patients included in the beta-adrenergic blocker trials received therapy with an ACEI. Survival benefit in the ACEI trials ranged from 12 to 33%, which was mainly a result of reduction in deaths from worsening HF. Meta-analyses of the beta-adrenergic blocker trials show a reduction in mortality of approximately 30 to 35%. It is felt that the use of an ACEI and beta-adrenergic blocker in patients with HF is synergistic and should be used in combination whenever possible.

See Table 5 titled "Adrenergic Blockers in Patients with Systolic HF" in the original guideline document.

Caution should be exercised when initiating these agents in patients with HF. Initial dosages should be low and titrated upward slowly and as tolerated. Patients can become transiently worse with each dosage increase. Since patients may experience fluid retention during initiation, daily weights are recommended with corresponding adjustments in diuretic dose. Some patients may also experience fatigue or weakness that may resolve after several weeks or require dosage adjustments. Another factor that may contribute to a need for a delay in titration is a low heart rate. Clinicians who do not have experience with beta-adrenergic blockers in patients with HF should consult with a cardiologist. It is important that patients with HF on a beta-adrenergic blocker are titrated carefully to a target dose as used in clinical trials (refer to Table 6 in the original guideline document) or as tolerated.

Factors that appear to contribute to a beneficial response are selection of patients who are clinically stable (i.e., not hospitalized in intensive care, no or minimal evidence of volume overload or depletion, no recent treatment with intravenous positive inotropic agents) when therapy starts, a low initial dosage, a gradual increase in the dosage (2 week intervals), and an adequate duration of treatment (3 to 12 months before effects are seen).

Beta-adrenergic blockers should not be used in patients with bronchospastic disease, symptomatic bradycardia, or advanced heart block without a pacemaker. Caution should be used in patients with asymptomatic bradycardia with a HR of less than 60 bpm. If the patient is on digoxin with a HR of less than 60 bpm, reconsider digoxin in favor of the benefits of a beta-adrenergic blocker, or consider referral to a cardiologist for adjustment in therapy. It should be noted that patients with DM or chronic obstructive pulmonary disease were not excluded from the clinical trials.

Common drug interactions are listed in Appendix B of the original guideline document.

See Table 6 titled "Adrenergic Blockers" in the original guideline document.

Pharmacologic recommendations for beta-adrenergic blockers in patients with HF:

Strength of Recommendation and Evidence Rating

Grade A (always indicated and acceptable):

- Use a beta-adrenergic blocker in patients with stable HF (Stage C) on standard therapy. (Overall Quality: Good; Net Effect: Substantial; ACC/AHA Recommendations: Class I; Evidence Level: A) ("Effect of metoprolol CR/XL," 1999; "The Cardiac Insufficiency Bisoprolol Study (CIBIS-II)," 1999; Packer et al., 1996; Packer et al., 2001; Packer et al., 2002; Leizorovicz et al., 2002; Shibata, Flather, & Wang, 2001)

Grade B (may be useful/ effective):

- None

Grade C (may be considered):

- None

Grade D (may not be useful/ effective; possibly harmful):

- None

Grade I (insufficient evidence to recommend for or against):

- None

#### J. Angiotensin II Receptor Antagonists (AIIRAs)

##### Objective

To provide recommendations for the appropriate use of AIIRAs (also referred to as ARBs) in patients with a diagnosis of systolic HF

##### Annotation

ACEIs reduce levels of angiotensin II, a potent vasoconstrictor, and inhibit the breakdown of bradykinin, a vasodilator. Production of angiotensin II also occurs through alternative pathways. The AIIRAs, on the other hand, selectively block the angiotensin II type1 receptor so that the effects of angiotensin II are blocked regardless of how it is produced. The AIIRAs do not inhibit the angiotensin II type 2 receptor, which is thought to have beneficial effects such as vasodilation and inhibition of proliferative and hypertrophic responses. The AIIRAs do not affect bradykinin, which is thought to be responsible for the cough that occurs in up to 39% of patients taking an ACEI. The incidence of cough in patients treated with an AIIRA is similar to that with placebo. The contribution of bradykinin to the favorable results of the ACEI trials in HF patients is unknown, but may be as important as suppression of angiotensin.

In the ELITE (Evaluation of Losartan in the Elderly) Study, the AIIRA losartan was compared to an ACEI, captopril, in 722 patients with NYHA class II to IV

HF and LVEF <40%. Patients were randomized to losartan (up to 50 mg) once daily or captopril (up to 50 mg) three times daily for 48 weeks. Seventy-five percent of patients in the losartan group and 71% of patients in the captopril group received target doses. The majority of patients were prescribed diuretics, and 55% were taking digoxin at the time of study enrollment. The primary endpoint of the study was the effect of treatment on serum Cr ( $\geq 0.3$  mg/dL increase). There was no difference between treatment groups in the rise in serum creatinine during continued treatment. Death and/or hospitalization for HF occurred in 9.4% of patients on losartan and 13.2% on captopril (32% risk reduction,  $P = 0.075$ ). These results were primarily due to a 46% decrease in all-cause mortality in patients on losartan compared to patients on captopril ( $P = 0.035$ ), primarily due to a reduction in sudden cardiac death. The two treatment groups did not differ in the frequency of hospital admission for HF. NYHA functional class improved significantly and similarly compared to baseline for both groups. More patients in the captopril group (20.8%) withdrew from the study due to adverse events compared to patients in the losartan group (12.2%). Cough was reported in 3.8% of patients taking 28 captopril compared to 0% in losartan treated patients. The favorable mortality rate in the losartan group was not hypothesized a priori. Therefore, replication of the results was attempted in ELITE II.

ELITE II enrolled 3,152 HF patients to evaluate the effects of losartan 50 mg once daily compared to captopril 50 mg three times daily on overall mortality and cardiac events (sudden cardiac death or resuscitated cardiac arrest). There was no significant difference in all-cause mortality between the treatment groups (17.7% on losartan vs. 15.9% on captopril,  $P = 0.16$ ). There was no difference between the groups in sudden death or resuscitated cardiac arrest or hospital admissions. However, this was a superiority trial not designed to detect equivalence between groups. Therefore, losartan and captopril cannot be concluded to be the same. Patients receiving captopril had significantly more adverse effects resulting in discontinuation of the drug than patients on losartan ( $P < 0.001$ ).

The RESOLVD Pilot Study compared candesartan, enalapril, and the combination of the two agents in 768 patients with NYHA class II to IV HF with a LVEF <40%. Patients were placed on candesartan (4, 8, or 16 mg), candesartan (4 or 8 mg) plus enalapril (20 mg), or enalapril (20 mg) for 43 weeks. The primary endpoints were exercise tolerance, ventricular function, quality of life, neurohormone levels, and tolerability. There was no significant difference between the treatment groups in results of the six-minute walk test, NYHA functional class, or quality of life. There was a trend toward an increase in ejection fraction, although not significant, in the patients treated with candesartan and enalapril compared to patients on candesartan or enalapril. End-diastolic and end-systolic volumes increased less with combination therapy compared with patients on candesartan or enalapril alone. There appeared to be a benefit of combination therapy on the patient's neurohormonal profile. Although not powered to evaluate morbidity and mortality, another analysis suggested that there might be an increase in HF hospitalizations in the patients receiving candesartan by 3-way group comparison.

More recently, the results of the Val-HeFT (Valsartan Heart Failure Treatment) study were published. The trial included 5,010 patients with NYHA class II (62%), III (36%), or IV (2%) HF on standard therapy (diuretics: 85%; ACEI: 93%; beta-adrenergic blockers: 35%; and digoxin 67%). Baseline LVEF was 27%. Patients were randomized to therapy with either valsartan (40 mg twice daily, titrated to a target of 160 mg twice daily) or placebo. Mean follow-up was 23 months. The two primary endpoints were mortality and the combined endpoint of mortality and morbidity (i.e., cardiac arrest with resuscitation, HF hospitalization, or intravenous inotropic agents or vasodilators for over 4 hours). Overall mortality was similar, occurring in 19.7% of patients in the valsartan group and 19.4% of patients on placebo ( $P = 0.80$ ). The combined primary endpoint occurred in 28.8% and 32.1% of patients on valsartan and placebo, respectively (RR 0.87 CI 0.77-0.97,  $P = 0.009$ ; ARR 3.3%; NNT = 30.3). This included a reduction in hospitalizations for HF (13.8% valsartan vs. 18.2% placebo; ARR 4.4%; NNT = 22.7). However, death from any cause (as first event) was higher in patients on valsartan compared to patients receiving placebo (14.2% vs. 12.6%, respectively). According to a subgroup analysis, there was an increased risk of mortality ( $P = 0.0009$ ) and a trend toward an increased risk of combined morbidity and mortality ( $P = 0.10$ ) in patients receiving valsartan in conjunction with an ACEI and beta-adrenergic blocker. Patients who were not on an ACEI or beta-adrenergic blocker experienced a significant reduction in mortality ( $P = 0.012$ ). Patients on valsartan but not on an ACEI (with or without a beta-adrenergic blocker) had a lower risk of death (RR 0.67, CI 0.42-1.06) and a lower risk of the combined endpoint (RR 0.56, CI 0.39-0.81). A subanalysis of the 366 patients in Val-HeFT who were not on an ACEI was recently published. In these patients there was a 33% decrease in all-cause mortality ( $P = 0.017$ ) and a 53% decrease in combined morbidity and mortality ( $P < 0.001$ ). The authors conclude that valsartan is an appropriate alternative in patients who are unable to tolerate an ACEI for the treatment of HF.

The AIIRAs have yet to be shown to be equivalent or superior to the ACEIs in patients with HF. According to a recent meta-analysis of 12,469 patients, the AIIRAs were not found to be superior to an ACEI in reducing mortality or hospitalizations. There was a trend toward improved mortality and hospitalizations with an AIIRA compared to placebo in patients not on an ACEI, and the combination of an AIIRA and ACEI significantly reduced the risk of hospitalizations compared to patients on an ACEI alone. In a previous meta-analysis of 1,896 patients, losartan contributed to a mortality benefit compared to a control group of either placebo or an ACEI, but this meta-analysis did not include the more recent outcome trials with an AIIRA in patients with HF.

An AIIRA should not be considered unless a patient is unable to tolerate an ACEI due to uncontrolled cough (or with caution in patients with history of angioedema; refer to discussion below). The benefit of an AIIRA in combination with an ACEI is still to be determined. Since the benefits of an ACEI in conjunction with a beta-adrenergic blocker is well-defined and there may be a detrimental effect in patients on an AIIRA with an ACEI and beta-adrenergic blocker, an AIIRA should not be used unless the patient is intolerant to an ACEI or unable to take a beta-adrenergic blocker. Additional information on the role of an AIIRA in patients with HF may be determined

with the results of CHARM (candesartan in HF-assessment of reduction in mortality and morbidity).

The incidence of cough is estimated to be anywhere from 0 to 39% in patients treated with an ACEI. In SOLVD, cough was reported in 37% of patients treated with enalapril compared to 31% of patients randomized to placebo. In V-HeFT II, 37% of patients on enalapril complained of cough compared to 29% receiving hydralazine/isosorbide dinitrate (HYD/ISDN). The incidence of cough associated with the AIIRAs is similar to placebo (2.6 to 3.4% vs. 1.5 to 3.3%). In the ELITE Study, 3.8% of patients on an ACEI withdrew from the study due to complaints of cough compared to 0% of patients treated with an AIIRA. Use of an AIIRA can be considered in patients who are unable to tolerate treatment with an ACEI due to cough, although there is a slight chance that patients may develop a cough with an AIIRA.

The incidence of angioedema in patients taking ACEIs is approximately 0.1 to 1.2%. It has been reported that black American patients have an increased relative risk of 4.5 of angioedema associated with use of an ACEI compared to white patients. There are at least 20 published case reports of angioedema in patients treated with an AIIRA. In over one-third of these cases, the patients previously experienced angioedema with an ACEI. Almost 100 cases have been reported to the Therapeutic Goods Administration of Australia as of April 2001. Therefore, if an AIIRA is considered appropriate in a patient who has previously experienced angioedema, it should be used with caution.

The angiotensin II receptor antagonists, like the ACEIs, decrease release of aldosterone from the adrenal cortex, which can lead to potassium reabsorption. It is unclear at this time if treatment with an AIIRA would be an appropriate alternative in patients who develop hyperkalemia on an ACEI. In SOLVD, hyperkalemia with potassium levels greater than 5.5 mmol/L was reported in 6.4% of patients on enalapril compared to 2.5% of patients on placebo. In the ELITE Study, an increase in serum potassium of  $\geq 0.5$  mmol/L above baseline was observed in 22.7% patients receiving captopril compared to 18.8% of patients on losartan. The proportion of patients with potassium levels  $\geq 5.5$  mmol/L did not differ significantly among the treatment groups in the RESOLVD Pilot Study. The VAL-K Study Group reported that the change in serum potassium was not significantly different in patients on lisinopril compared to valsartan with mild renal insufficiency. In patients with moderate renal insufficiency with a glomerular filtration rate (GFR)  $\leq 60$  mL/min/1.73 m<sup>2</sup>, there was a significant increase of 0.28 mEq/L ( $P = 0.04$ ) above baseline (4.6 mEq/L). The increase of 0.12 mEq/L seen with valsartan in this subgroup was not significant ( $P = 0.1$ ). Therefore, if use of a diuretic is contraindicated or is not effective in reducing hyperkalemia, an AIIRA may be considered instead of an ACEI, under close monitoring, in patients with moderate renal insufficiency who develop hyperkalemia on an ACEI.

Patients receiving an AIIRA in conjunction with potassium supplements or potassium-sparing diuretics (including spironolactone) may result in an increased potassium level. Other clinically significant drug interactions with the AIIRAs are listed in Appendix B of the original guideline document.

See Table 7 titled "Angiotensin II Receptor Antagonists" in the original guideline document.

Pharmacologic recommendations for AIIRAs in patients with HF:

Strength of Recommendation and Evidence Rating

Grade A (always indicated and acceptable):

- None

Grade B (may be useful/effective):

- Use an AIIRA in patients on standard therapy who cannot tolerate an ACEI due to cough and possibly angioedema. (Overall Quality: Fair; Net Effect: Moderate; ACC/AHA Recommendations: Class IIa; Evidence Level: A) (Pitt et al., 1997; Pitt et al., 2000; McKelvie et al., 1999; Greenberg, 1999; Cohn & Tognoni, 2001; Maggioni et al., 2002; Jong et al., 2002; Sharma et al., 2000; Hunt et al., 2001)

Grade C (may be considered):

- Use an AIIRA in addition to an ACEI in patients with HF, if not on a beta-adrenergic blocker. (Overall Quality: Fair; Net Effect: Moderate; ACC/AHA Recommendations: Class IIb; Evidence Level: B) (Cohn & Tognoni, 2001; Jong et al., 2002; Hunt et al., 2001; Struckman & Rivey, 2001)

Grade D (may not be useful/ effective; possibly harmful):

- Use an AIIRA instead of an ACEI in patients who are able to tolerate an ACEI. (Overall Quality: Fair; Net Effect: Negative; ACC/AHA Recommendations: Class III; Evidence Level: B) (Pitt et al., 1997; Pitt et al., 2000; McKelvie et al., 1999; Greenberg, 1999; Cohn & Tognoni, 2001; Jong et al., 2002; Sharma et al., 2000; Hunt et al., 2001)
- Use an AIIRA before a beta-adrenergic blocker in patients who are unable to tolerate an ACEI. (Overall Quality: Fair; Net Effect: Negative; ACC/AHA Recommendations: Class III; Evidence Level: A) (Cohn & Tognoni, 2001; Hunt et al., 2001)

Grade I (insufficient evidence to recommend for or against):

- None

K. Hydralazine/Isosorbide Dinitrate

Objective

To provide recommendations for the appropriate use of HYD/ISDN in patients with a diagnosis of systolic HF

## Annotation

Patients with contraindications to or who cannot tolerate an ACEI present a dilemma since ACEIs are the preferred agents for afterload reduction. While no studies have specifically addressed the combination of HYD/ISDN in patients with HF who cannot tolerate ACEIs, treatment with HYD/ISDN has been shown to reduce mortality by two years compared to placebo (risk reduction 34%, CI 0.04 to 0.54,  $P < 0.028$ ; ARR 5.29%; NNT = 18.9). A similar mortality rate was found in another study in HF patients (majority with NYHA class II or III HF) treated with HYD/ISDN compared with an ACEI, although mortality after two years was lower in patients treated with an ACEI compared with patients on HYD/ISDN (risk reduction 28.2%,  $P = 0.016$ ; ARR 7.0%; NNT=14.3). As discussed in Annotation H, there may be racial differences in response to therapy with the ACEIs, where black patients may not derive as much benefit as seen in white patients. The opposite may occur with HYD/ISDN, where there has been a greater benefit in black patients compared to white patients. It is unknown at this time if recommendations for HF therapy should be modified based on these findings.

Peripheral vasodilators such as HYD (arterial vasodilator) and ISDN (venodilator) can produce favorable hemodynamic effects in patients with HF. Although the benefit of HYD/ISDN in combination with an ACEI and/or a beta-adrenergic blocker has not been evaluated, this combination may be considered in patients who do not achieve adequate response with standard therapy.

Side-effects such as headache, tachycardia, flushing, hypotension, and edema, as well as dosing frequency, preclude the use of this regimen in as many as one-third of patients. Other adverse effects reported with hydralazine include rash, arthralgia, and other lupus-like symptoms. Common drug interactions are listed in Appendix B of the original guideline document.

See Table 8 titled "Use of HYD/ISDN in Patients with Systolic Dysfunction" in the original guideline document.

### Pharmacologic recommendations for HYD/ISDN in patients with HF:

#### Strength of Recommendation and Evidence Rating

Grade A (always indicated and acceptable):

- None

Grade B (may be useful/ effective):

- Use HYD/ISDN (in patients on standard therapy) in patients intolerant to ACEIs, especially for those with hypotension, renal insufficiency, and possibly angioedema on an ACEI. (Overall Quality: Fair; Net Effect: Moderate; ACC/AHA Recommendations: Class IIa; Evidence Level: B) (Hunt et al., 2001; Agency for Health Care Policy and Research [AHCPR], 1994; Cohn et al., 1986; Cohn et al., 1991)

Grade C (may be considered):

- Use HYD/ISDN in patients already taking an ACEI and beta-adrenergic blocker. (Overall Quality: Poor; Net Effect: Small; ACC/AHA Recommendations: Class IIb; Evidence Level: B) (Cohn et al., 1986; Cohn et al., 1991)

Grade D (may not be useful/effective; possibly harmful):

- Use HYD/ISDN to reduce mortality in patients who have not been given a trial of an ACEI and/or beta-adrenergic blocker (Overall Quality: Fair; Net Effect: Negative; ACC/AHA Recommendations: NA; Evidence Level: NA) (Hunt et al., 2001; Agency for Health Care Policy and Research (AHCPR), 1994; Cohn et al., 1986; Cohn et al. 1991)

Grade I (insufficient evidence to recommend for or against):

- None

#### L. Digoxin

##### Objective

To provide recommendations for the appropriate use of digoxin in patients with a diagnosis of systolic HF

##### Annotation

Digoxin is thought to be beneficial in patients with systolic HF through inhibition of sodium-potassium adenosine triphosphatase resulting in increased contractility of the heart and reduced activation of the neurohormonal system. The use of agents with positive inotropic activity as the mainstay of therapy for HF has decreased over the years. This has primarily been due to the increased mortality associated with some of the agents in this class. Digoxin continues to have a role in the treatment of patients with HF by improving patient symptoms and decreasing hospitalizations and not adversely affecting survival.

According to a meta-analysis, treatment with digoxin in patients with HF due to systolic dysfunction can reduce the incidence of clinical deterioration by 12% compared to patients on placebo. The Randomized Assessment of (the effect of) Digoxin on Inhibitors of the Angiotensin-Converting Enzyme (RADIANCE) Study evaluated 178 patients with NYHA class II or III HF stabilized on digoxin, diuretics, and an ACEI. Patients were randomized to continuation of treatment or withdrawal of digoxin therapy for 12 weeks. Patients who were withdrawn from digoxin experienced worsening HF ( $P < 0.001$ ) and a decreased exercise tolerance ( $P = 0.033$ ), worsening NYHA class ( $P = 0.019$ ), decreased quality of life ( $P = 0.04$ ) and LVEF ( $P = 0.001$ ; digoxin  $0.27 \pm 0.01$  and  $0.26 \pm 0.01$  compared to placebo  $0.30 \pm 0.01$  and  $0.26 \pm 0.01$ , before and after treatment, respectively). The Prospective

Randomized Study of Ventricular Failure and the Efficacy of Digoxin (PROVED) trial was a study evaluating 88 patients with NYHA class II or III HF on digoxin and diuretics and the effect of digoxin withdrawal or continuation of therapy. Patients who had digoxin withdrawn experienced a worsening of maximum exercise performance, a higher percentage of treatment failures, and a decreased time to treatment failure.

These trials demonstrate the benefit of digoxin in reducing symptoms associated with mild to moderate HF. The Digitalis Investigators Group (DIG) trial evaluated the benefit of digoxin on survival. This trial enrolled 6,800 patients on diuretics and an ACEI who were randomized to receive digoxin or placebo for a mean of 37 months. The results showed that treatment with digoxin significantly decreased the risk for hospitalizations due to HF by 28%, although there was no significant reduction in mortality with digoxin treatment. In a recent post hoc analysis of the DIG trial, a decrease in the rate of cardiovascular deaths and deaths from worsening HF was found in the men ( $n = 5,281$ ), but not in the women who were treated with digoxin ( $n = 1,519$ ). The death rate in women on digoxin was higher than women randomized to placebo (33.1% vs. 28.9%, respectively;  $P = 0.078$ ). There was a decrease in hospitalizations for worsening HF in women on digoxin compared to women on placebo (30.2% vs. 34.4%, respectively;  $P = 0.079$ ). Due to these findings, the authors suggest that the role of digoxin in women be reevaluated. Others suggest that a lower dose with a resultant serum concentration  $<1$  ng/mL be used as there was a significant difference in the digoxin concentration (random measurement in approximately one-third of patients at 1 month) that may have accounted for the difference in outcome (0.9 ng/mL in women vs. 0.8 ng/mL in men;  $P = 0.007$ ).

Digoxin is recommended in patients with symptomatic HF, without bradycardia, to improve clinical status and thereby decrease the risk of hospitalization due to HF. Treatment is usually initiated in conjunction with a diuretic, ACEI, and beta-adrenergic blocker since these latter two classes of agents have been shown to improve survival in patients with HF. If there is no symptomatic improvement after one to two months of therapy, the risk versus benefit of continued digoxin therapy should be considered. Digoxin is the drug of choice to control rapid ventricular response in patients with systolic dysfunction and atrial fibrillation.

Loading doses are not necessary for patients in normal sinus rhythm. The most commonly prescribed dose of digoxin is 0.125 to 0.25 mg/day. Initial dosing should be conservative (e.g., 0.125 mg every day [qd] or every other day [qod]) especially for patients with reduced CrCl, decreased weight, and/or decreased muscle mass. The utility of monitoring serum digoxin levels to assess efficacy has not been established. Subgroup analysis from the DIG trial as well as in the Prospective Randomized Milrinone Survival Evaluation (PROMISE) trials showed that higher concentrations (even within the therapeutic range) were associated with an increased risk of mortality. In both the RADIANCE and PROVED trials, the mean digoxin serum concentration was 1.2 ng/mL, and in the DIG trial the mean serum digoxin level was 0.8 ng/mL at 12 months. In a meta-analysis of the PROVED and RADIANCE trials, the clinical efficacy (e.g., worsening HF, change in LVEF, treadmill time) of low (0.5-0.9 ng/mL), moderate (0.9-1.2 ng/mL), and high

(>1.2 ng/mL) serum digoxin concentrations were compared. There was no relationship between the endpoints and the three groups. The authors concluded that lower levels may therefore provide similar outcomes without the risk of detrimental effects seen with higher levels although levels are not typically drawn unless monitoring for toxicity.

In general, trough (or a minimum of 6 hours post dose due to distribution) serum digoxin levels should be monitored if any of the following occurs:

1. HF worsens or renal function deteriorates.
2. Signs of toxicity develop (e.g., confusion, nausea, vomiting, abdominal pain, diarrhea, anorexia, fatigue, arrhythmias, visual disturbances).
3. Dose adjustments are made.
4. Additional medications are added that affect the serum digoxin concentration (e.g., quinidine, verapamil, amiodarone, antibiotics, anticholinergics) (refer to Appendix B of the original guideline document).

#### Pharmacologic recommendations for digoxin in patients with HF:

##### Strength of Recommendation and Evidence Rating

Grade A (always indicated and acceptable):

- Use digoxin to improve functional status and reduce frequency of hospitalizations if continued symptoms on a diuretic and ACEI. (Overall Quality: Good; Net Effect: Moderate; ACC/AHA Recommendations: Class I; Evidence Level: A) (Hunt et al., 2001; "The effect of digoxin," 1997; "Comparative effects of therapy with captopril," 1988; Jaeschke, Oxman, & Guyatt, 1990; Packer et al., 1993; Uretsky et al., 1993; Rathone, Wang, & Krumholz, 2002; Eichhorn & Gheorghiade, 2002)

Grade B (may be useful/effective):

- None

Grade C (may be considered):

- None

Grade D (may not be useful/effective; possibly harmful):

- Use digoxin in patients in normal sinus rhythm who are not on an ACEI and beta-adrenergic blocker (Overall Quality: Good; Net Effect: Negative; ACC/AHA Recommendations: NA; Evidence Level: NA) (Hunt et al., 2001; "The effect of digoxin," 1997; "Comparative effects of therapy with captopril," 1988; Jaeschke, Oxman, & Guyatt, 1990; Packer et al., 1993; Uretsky et al., 1993; Rathone, Wang, & Krumholz, 2002; Eichhorn & Gheorghiade, 2002)

- Use digoxin to improve survival in patients with HF (Overall Quality: Good; Net Effect: Zero; ACC/AHA Recommendations: NA; Evidence Level: NA) ("The effect of digoxin," 1997; "Comparative effects of therapy with captopril," 1988)

Grade I (insufficient evidence to recommend for or against):

- None

#### M. Aldosterone Antagonists

##### Objective

To provide recommendations for the appropriate use of aldosterone antagonists in patients with a diagnosis of systolic HF

##### Annotation

Aldosterone antagonists (e.g., spironolactone) competitively inhibit the effects of aldosterone. One of the proposed mechanisms for benefit of using ACEIs in patients with HF is that of suppression of production of aldosterone. Additional therapy with an aldosterone antagonist was originally felt not to be necessary and could cause an increase in the risk of hyperkalemia due to potential for potassium retention if aldosterone is decreased. Evidence has shown that addition of an aldosterone antagonist may be beneficial in patients with severe HF (recent NYHA class IV HF and current class III or IV symptoms and LVEF  $\leq 35\%$ ), even in patients already receiving an ACEI. This suggests that therapy with an ACEI may not achieve long-term suppression of aldosterone production. There is insufficient evidence to make a recommendation as to the use of aldosterone antagonists in patients with mild to moderate HF.

These recommendations are based on a study that enrolled 1,663 patients with severe class IV HF within the last 6 months (and class III or IV at time of enrollment), a LVEF  $\leq 35\%$  within the last 6 months, and treated with conventional therapy (95% ACEI, 100% loop diuretic, 75% digoxin). In addition, 11% of patients were on a beta-adrenergic blocker. Patients were randomized to spironolactone 25 mg once daily or placebo. The primary endpoint was to evaluate all-cause mortality. After a mean follow-up of 24 months, the trial was discontinued early due to a 30% reduction in the risk of death due to progressive HF and sudden death of a cardiac cause in patients in the spironolactone group (RR 0.70, 95% CI 0.60-0.82,  $P < 0.001$ ; ARR 11.4%; NNT = 8.8). Patients on spironolactone also had a 35% decrease in hospitalizations due to worsening HF ( $P < 0.001$ ) and experienced a significant improvement in symptoms ( $P < 0.001$ ) resulting in some patients dropping into a lower NYHA class.

These are highly complex patients with a high mortality rate and should be cared for by a multidisciplinary HF team including a primary care provider in consultation with a cardiologist. The risk versus benefit of using spironolactone in these patients needs to be determined. Spironolactone may contribute to serious hyperkalemia if not used properly in patients with HF.

In addition to gastrointestinal side effects, aldosterone antagonists can cause gynecomastia, hyperkalemia, and menstrual irregularities. In the study, gynecomastia or breast pain was reported in 10% of male patients in the spironolactone group. The incidence of hyperkalemia was not significant. However, it should be noted that patients with serum creatinine >2.5 mg/dL and serum potassium >5.0 mmol/L were excluded from the study and patients were not taking other potassium-sparing diuretics. Hyperkalemia occurs more frequently in patients receiving potassium supplements and in patients with renal insufficiency. Use of potassium supplements with spironolactone should be avoided unless hypokalemia develops. Spironolactone should be used with caution in patients with renal insufficiency; patients should be scheduled for follow-up electrolytes and renal function after initiation and dose adjustments. Spironolactone should also be used with caution in patients receiving ACEIs due to the potential for hyperkalemia; potassium should be monitored closely in these patients. Serum potassium should be monitored at 1 week and every 4 weeks for the first 3 months, then every 3 months for the first year and every 6 months thereafter. More frequent monitoring may be indicated in patients on concomitant medications that may increase potassium levels, with renal insufficiency or DM, who are of advanced age, experiencing worsening HF or conditions that may contribute to dehydration. If the potassium increases to >5.4 mmol/L, the dose of spironolactone should be reduced. If serious hyperkalemia develops, spironolactone should be discontinued.

The initial dose of spironolactone used was 25 mg once daily. The dose was decreased to 25 mg every other day in patients exhibiting hyperkalemia. The dose was increased to 50 mg once daily at 8 weeks in patients who had signs or symptoms of worsening HF and did not have hyperkalemia. Patients receiving 50 mg spironolactone should have their serum potassium measured one week after the dose was increased, and then follow-up as described above. Refer to Appendix B of the original guideline document for common drug interactions.

#### Pharmacologic recommendations for spironolactone in patients with HF:

##### Strength of Recommendation and Evidence Rating

##### Grade A (always indicated and acceptable):

- None

##### Grade B (may be useful/effective):

- Low dose (12.5 to 25 mg/d) spironolactone in patients with severe HF (recent NYHA class IV HF and current class III or IV symptoms), provided the potassium is normal (<5 mmol/L) and renal function adequate (serum Cr  $\leq$  2.5 mg/dL) (Overall Quality: Good; Net Effect: Substantial; ACC/AHA Recommendations: Class IIa; Evidence Level: B) (Hunt et al., 2001; Pitt et al., 1999)

##### Grade C (may be considered):

- None

Grade D (may not be useful/effective; possibly harmful):

- None

Grade I (insufficient evidence to recommend for or against):

- None

#### N. Continue Present Management and Schedule Regular Follow-up

##### Objective

To provide recommendations for appropriate follow-up of patients with a diagnosis of systolic HF

##### Annotation

Patients should be scheduled for regular follow-up in order to provide the most effective care. At each encounter, an inquiry should be made as to the patient's adherence to the medication regimen and nonpharmacologic measures and adverse effects to therapy. The patient should also be assessed for any change in functional status.

Patients should also be scheduled for routine monitoring of electrolytes and renal function. Evaluation of the patient's serum potassium is important due to the influence of medications on this parameter. There is the potential for hypokalemia with diuretics that may lead to toxicity in a patient receiving digoxin. The ACEIs, AIIRAs, and spironolactone may all increase potassium, leading to potential toxicity.

Adherence to the medication regimen is often not optimal and may lead to clinical deterioration in patients with HF. Patients need to be educated on the importance of adherence to the medication regimen in order to derive the benefits of decreased morbidity and mortality. The reason for not taking a medication as prescribed should be investigated. If it is a result of an adverse effect, the dosage of the medication can be adjusted or another class of medication considered.

Proper education of patients and their family is imperative so that they may have an understanding of the cause of HF, prognosis, therapy, dietary restrictions, activity, adherence, and the signs and symptoms of recurrent HF. If patients and/or caregivers are cognizant of the signs and symptoms of recurrent HF, they may have the opportunity to present to the health care practitioner before the patient's condition deteriorates. Patients and caregivers should also be educated on the patient's prognosis for function and survival. Treatment options, a living will, and advanced directives should be discussed with the patient and caregiver in response to different events that may occur. The availability of hospice care should also be discussed.

Continuity of care is important for the patient's overall care and for the implementation of the patient's request for end of life care.

Some facilities may have interdisciplinary HF disease management clinics to provide continuity of care and improve outcomes for patients with HF.

#### Definitions:

The rating scale used for this document was based on the evidence rating of the U.S. Preventive Services Task Force.

#### Quality of Evidence

I: Evidence obtained from at least one properly randomized controlled trial

II-1: Evidence obtained from well-designed controlled trials without randomization

II-2: Evidence obtained from well-designed cohort or case-control analytic studies

II-3: Evidence obtained from multiple time series studies; dramatic results in uncontrolled experiments

III: Opinions of respected authorities, descriptive studies and case reports; reports of expert committees

#### Overall Quality

Good: High grade evidence (I or II-1) directly linked to health outcome

Fair: High grade evidence (I or II-1) linked to intermediate outcome or moderate grade evidence (II-2 or II-3) directly linked to health outcome

Poor: Level III evidence or no linkage of evidence to health outcome

#### Net Effect of Intervention

##### Substantial:

- More than a small relative impact on a frequent condition with a substantial burden of suffering, or
- A large impact on an infrequent condition with a significant impact on the individual patient level

##### Moderate:

- A small relative impact on a frequent condition with a substantial burden of suffering, or

- A moderate impact on an infrequent condition with a significant impact on the individual patient level

Small:

- A negligible relative impact on a frequent condition with a substantial burden of suffering, or
- A small impact on an infrequent condition with a significant impact on the individual patient level

Zero or Negative:

- Negative impact on patients, or
- No relative impact on either a frequent condition with a substantial burden of suffering, or
- An infrequent condition with a significant impact on the individual patient level

Strength of Recommendation

A: A strong recommendation that the intervention is always indicated and acceptable

B: A recommendation that the intervention may be useful/effective

C: A recommendation that the intervention be considered

D: A recommendation that an intervention may be considered not useful/effective, or may be harmful

I: Insufficient evidence to recommend for or against; clinical judgment should be used

The evidence rating system used in the American College of Cardiology/American Heart Association (ACC/AHA) Practice Guidelines on the Evaluation and Management of HF are included below. As this is used by ACC/AHA guidelines, this format will also be included in the recommendations to assist in the application of the recommendations to clinical practice.

Class I: Conditions for which there is evidence and/or general agreement that a given procedure/therapy is useful and effective

Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about usefulness/efficacy of performing the procedure/therapy

Class IIa: Weight of evidence/opinion is in favor of usefulness/efficacy

Class IIb: Usefulness/efficacy is less well established by evidence/opinion

Class III : Conditions for which there is evidence and/or general agreement that a procedure/therapy is not useful/effective and in some cases may be harmful.

#### Level of Evidence

A: Data is derived from multiple randomized clinical trials.

B: Data is derived from a single randomized trial or nonrandomized studies.

C: Consensus opinion of experts is the primary source of recommendation.

#### Abbreviations

AIIRA (also ARB) - Angiotensin II receptor antagonist (also referred to as angiotensin receptor blocker)

ACC/AHA - American College of Cardiology/American Heart Association

ACEI - Angiotensin-converting enzyme inhibitor

ARR - Absolute risk reduction

AV - Atrioventricular

BNP - Brain natriuretic peptide

BUN - Blood urea nitrogen

CCB - Calcium channel blocker

CI 95% - confidence interval

Cr - Creatinine

CrCl - Creatinine clearance

DM - Diabetes mellitus

DOE - Dyspnea on exertion

HCTZ - Hydrochlorothiazide

HF - Heart failure

HTN - Hypertension

HYD - Hydralazine

INR - International normalized ration

ISDN - Isosorbide dinitrate

JVD - Jugular venous distention

K + - Potassium

LV - Left ventricular

LVEF - Left ventricular ejection fraction

LVEDP - Left ventricular end diastolic pressure

LVH - Left ventricular hypertrophy

MI - Myocardial infarction

NNT - Number needed to treat

NSAID - Non-steroidal anti-inflammatory drug

NYHA - New York Heart Association

PND - Paroxysmal nocturnal dyspnea

RR - Relative risk

SNS - Sympathetic nervous system

SOB - Shortness of breath

TSH - Thyroid-stimulating hormone (thyrotropin)

#### CLINICAL ALGORITHM(S)

An algorithm is provided in the original guideline document for the pharmacologic management of patients with heart failure.

## EVIDENCE SUPPORTING THE RECOMMENDATIONS

### REFERENCES SUPPORTING THE RECOMMENDATIONS

[References open in a new window](#)

### TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

Recommendations were based on evidence published in the medical literature. Where evidence was not available, expert opinion of the Medical Advisory Panel was used.

The type of supporting evidence is identified and graded for selected recommendations (see "Major Recommendations").

## BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

### POTENTIAL BENEFITS

Overall potential benefits include:

- Reduction in the development of heart failure in patients in Stage A Heart Failure
- Appropriate management of patients with chronic heart failure
- Improved symptoms
- Increased functional capacity
- Improved quality of life
- Slowed disease progression
- Decreased need for hospitalization
- Prolonged survival

More specifically:

- Angiotensin-converting enzyme inhibitors improve heart failure symptoms, functional status, and quality of life, while decreasing frequency of hospitalization and mortality.
- Some beta-adrenergic blockers reduce mortality and decrease the symptoms of heart failure.
- Digoxin reduces symptoms associated with heart failure and decreases the risk for hospitalizations due to heart failure but does not improve mortality.
- Hydralazine and isosorbide dinitrate increases exercise tolerance and lowers mortality from heart failure.
- Low dose spironolactone improves symptoms, decreases hospitalizations for worsening heart failure, and decreased mortality.

### POTENTIAL HARMS

Overall potential harms:

- Adverse effects of medications
- Drug interactions with agents used in heart failure (Note: Specific information about common drug interactions with agents used to manage heart failure is listed in Appendix B of the original guideline document.)

Examples of potential adverse effects:

- Hydralazine. Adverse effects may include dizziness, headache, lupus-like syndrome, nausea, tachycardia, and postural hypotension.
- Isosorbide dinitrate. Adverse effects may include flushing, headache, postural hypotension, rash, and an increase in ocular pressure. Caution is recommended in patients with glaucoma.
- Beta-adrenergic blockers. Carvedilol should be given with food to reduce the incidence of orthostatic hypotension; consider separating the angiotensin converter enzyme inhibitor, adjusting dose of diuretic, or temporary angiotensin converting enzyme inhibitor dose reduction if dizziness occurs. Caution should be used when using beta-adrenergic blockers in patients with systolic dysfunction.
- Digoxin. Signs of digoxin toxicity include confusion, nausea, vomiting, abdominal pain, diarrhea, anorexia, fatigue, arrhythmias, and visual disturbances.
- Diuretic therapy: Use thiazide diuretics cautiously in patients with poorly controlled diabetes mellitus, symptomatic benign prostatic hyperplasia, or in patients with increased risk of volume depletion.
- Angiotensin II receptor antagonists: All angiotensin II receptor antagonists are contraindicated in second and third trimester pregnancy due to potential neonatal/fetal morbidity and death. Use angiotensin II receptor antagonists with caution in patients with renal artery stenosis. Use telmisartan with caution in patients with hepatic impairment.

## CONTRAINDICATIONS

### CONTRAINDICATIONS

- Contraindications to warfarin include increased risk of bleeding, difficulty adhering to the medication regimen or regular international normalized ratio (INR) monitoring, current alcohol abuse, or falls.
- Specific contraindications to angiotensin-converting enzyme inhibitors (ACEI) include documented hypersensitivity to an ACEI, bilateral renal artery stenosis or renal artery stenosis in a solitary kidney, pregnancy, serum potassium > 5.5 mEq/L that cannot be reduced, and symptomatic hypotension.
- All angiotensin II receptor antagonists are contraindicated in second and third trimester pregnancy due to potential neonatal/fetal morbidity and death.

## QUALIFYING STATEMENTS

### QUALIFYING STATEMENTS

Guidelines should not be considered inclusive of all proper methods of care or exclusive of other methods of care reasonably directed at obtaining the same results. The ultimate judgment regarding the propriety of any course of conduct must be made by the clinician in light of individual patient situations.

## IMPLEMENTATION OF THE GUIDELINE

### DESCRIPTION OF IMPLEMENTATION STRATEGY

The guideline is available (in Portable Document Format [PDF]) via the [Veterans Affairs \(VA\) Pharmacy Benefits Management Web site](#).

The guideline developers recommended that a hard copy be kept on file in the medical libraries. Distribution to all clinicians who manage patients with heart failure is strongly recommended. Clinicians are encouraged to have a copy of the document or a summary of key points available for reference when treating patients with heart failure.

A summary of key points in a pocket card version has been developed by the Veterans Affairs Pharmacy Benefits Management-Medical Advisory Panel (PBM-MAP) in conjunction with the Employee Education Service and have been made available.

Continuing education programs (e.g., on-line review of guideline) have been developed.

Departmental and individual education at the facility is also encouraged.

### IMPLEMENTATION TOOLS

Clinical Algorithm  
Patient Resources  
Pocket Guide/Reference Cards  
Quality Measures

For information about [availability](#), see the "Availability of Companion Documents" and "Patient Resources" fields below.

### RELATED NQMC MEASURES

- [Heart failure: percent of patients with ejection fraction less than 40 and a principal discharge diagnosis of heart failure who were on angiotensin-converting enzyme inhibitor \(ACEI\) or angiotensin receptor blocker \(ARB\) prior to admission \(inpatient heart failure antecedent cohort\).](#)
- [Heart failure: percent of patients admitted for heart failure that had documentation of instruction for monitoring weight prior to admission \(inpatient heart failure antecedent cohort\).](#)

### RELATED QUALITY TOOLS

- [Pharmacologic Management of Patients with Heart Failure: Algorithm](#)

- [Department of Veterans Affairs/Department of Defense \(VA/DoD\) Clinical Practice Guideline for the Pharmacologic Management of Chronic Heart Failure Guideline Summary: Update 2003](#)
- [Department of Veterans Affairs/Department of Defense \(VA/DoD\) Clinical Practice Guideline for the Pharmacologic Management of Chronic Heart Failure Pocket Guide: Update 2003](#)
- [Department of Veterans Affairs/Department of Defense \(VA/DoD\) Clinical Practice Guideline for the Pharmacologic Management of Chronic Heart Failure Key Points Card: Update 2003](#)
- [Health Tips for Heart Failure](#)

## INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

### IOM CARE NEED

Living with Illness

### IOM DOMAIN

Effectiveness  
Patient-centeredness

## IDENTIFYING INFORMATION AND AVAILABILITY

### BIBLIOGRAPHIC SOURCE(S)

Veterans Health Administration, Department of Veterans Affairs. The pharmacologic management of chronic heart failure. Washington (DC): Veterans Health Administration, Department of Veterans Affairs; 2003 Aug. 45 p. [242 references]

### ADAPTATION

Not applicable: The guideline was not adapted from another source.

### DATE RELEASED

2001 Feb (revised 2003 Aug)

#### GUIDELINE DEVELOPER(S)

Department of Veterans Affairs - Federal Government Agency [U.S.]  
Veterans Health Administration - Federal Government Agency [U.S.]

#### SOURCE(S) OF FUNDING

United States Government

#### GUIDELINE COMMITTEE

Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

#### COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Medical Advisory Panel (MAP) for the Pharmacy Benefits Management Strategic Healthcare Group: The Medical Advisory Panel (MAP) comprises practicing Veterans Affairs (VA) and Department of Defense physicians from facilities across the nation: Thomas Craig, MD, Chief Quality and Performance Officer, Office of Quality and Performance Management, Department of Veterans Affairs, Washington DC; Gregory Dalack, MD, Chief, Psychiatry Service, VA Ann Arbor Healthcare System, Assistant Professor of Psychiatry, University of Michigan; LTC John Downs, MD, USAF, MC, Program Director, Internal Medicine Residency, Wilford Hall Medical Center, Lackland AFB, Texas; Thomas H. Dickinson, MD, Local Service Line Manager, Ambulatory Care Service Line, VAMC Brockton, MA; Michael Ganz, MD, Chief, Nephrology, Cleveland VAMC, Associate Professor of Medicine, Case Western Reserve University; Peter A. Glassman, MBBS, MSc, Staff Internist, Department of Medicine, VAMC West Los Angeles, Assistant Professor of Medicine, University of California, Los Angeles; Matt Goetz, MD, Chief, Infectious Diseases, VA Greater Los Angeles Healthcare System, West Los Angeles VAMC; C.B. Good, MD, MPH, Chairman, Medical Advisory Panel, Staff Physician, Department of Medicine, Pittsburgh VAMC, Associate Professor of Medicine and Pharmacology, University of Pittsburgh; Robert C. Goodhope, MD, MBA, Chief Medical Officer, VA Outpatient Clinic, Tallahassee, FL; Robert Hariman, MD, Director, Cardiac Electrophysiology, Hines VA Hospital, Professor of Medicine, Loyola University School of Medicine; William Korchik, MD, Director, Extended Care Center, Medical Director, Adult Day Health Care, Minneapolis VAMC, Assistant Professor of Medicine, University of Minnesota; John Pope, MD, Director, Mental Health, Colmery-O'Neil VAMC, Instructor of Psychopharmacology, Karl Menninger School of Psychiatry; Alexander Shepherd, MD, Professor of Medicine and Pharmacology, University of Texas Health Science Center, San Antonio, TX

Pharmacy Benefits Management (PBM) Strategic Healthcare Group (SHG): John E. Ogden, RPh, MS, FASHP, Chief Consultant, PBM-SHG; Virginia S. Torrise, PharmD, Deputy Chief Consultant, PBM-SHG; Michael Valentino, RPh, MHSA, Associate Chief Consultant, PBM-SHG; Joe Canzolino, RPh, Assistant Chief Consultant, PBM-SHG; Fran Cunningham, PharmD, Program Manager, Pharmacoepidemiologic and Outcomes Research; Muriel Burk, PharmD, Clinical Pharmacy Specialist,

Pharmacoepidemiologic and Outcomes Research; Suzanne Lenz, RPh, Pharmacist Specialist/Contract Liaison; Elaine Furmaga, PharmD, Clinical Pharmacy Specialist; Mark Geraci, PharmD, BCOP, Clinical Pharmacy Specialist; Francine Goodman, PharmD, BCPS, Clinical Pharmacy Specialist; Cathy Kelley, PharmD, Clinical Pharmacy Specialist; Deborah Khachikian, PharmD, Clinical Pharmacy Specialist; Kathy Tortorice, PharmD, BCPS, Clinical Pharmacy Specialist; Lisa Torphy, Program Specialist

#### FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

#### GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Veterans Health Administration, Department of Veterans Affairs. The pharmacologic management of chronic heart failure. Washington (DC): Veterans Health Administration, Department of Veterans Affairs; 2002 Dec. 44 p.

#### GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the [Department of Veterans Affairs Web site](#).

Print copies: Department of Veterans Affairs, Veterans Health Administration, Office of Quality and Performance (10Q) 810 Vermont Ave. NW, Washington, DC 20420.

#### AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- The pharmacologic management of chronic heart failure pocket guide. Washington (DC): Department of Veterans Affairs (U.S.); 2003
- The pharmacologic management of chronic heart failure guideline summary. Washington (DC): Department of Veterans Affairs (U.S.); 2003
- PBM-MAP The pharmacologic management of chronic heart failure (HF) key points card - update 2003. Washington (DC): Department of Veterans Affairs (U.S.); 2003. 2 p.

Electronic copies available from the [Department of Veterans Affairs \(VA\) Web site](#).

Print copies: Department of Veterans Affairs, Veterans Health Administration, Office of Quality and Performance (10Q) 810 Vermont Ave. NW, Washington, DC 20420.

#### PATIENT RESOURCES

The following is available:

- Health tips for heart failure. Washington (DC): Department of Veterans Affairs (U.S.); 2003. 2 p.

Electronic copies available from the [Department of Veterans Affairs \(VA\) Web site](#).

Print copies: Department of Veterans Affairs, Veterans Health Administration, Office of Quality and Performance (10Q) 810 Vermont Ave. NW, Washington, DC 20420.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

## NGC STATUS

This summary was completed by ECRI on December 11, 2001. The summary was updated by ECRI on August 11, 2004.

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